UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 25 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Risk Assessment Review Committee Meeting on Difenoconazole

FROM: Brenda Tarplee
Risk Assessment Review Committee
Health Effects Division (7509C)

TO: Addressees

Attached for your review is the risk assessment document on Difenoconazole prepared by Dana Vogel

A meeting to review the Risk Assessment of this chemical is scheduled for Tuesday December 1, 1998 at 1:00 pm in Room 817, CM2.

Addressees

Bill Burnam
Donna Davis
Paula Deschamp
Jeff Evans
Roger Gardner
Ray Kent
Steve Knizner
Tim McMahon
Mike Metzger
David Miller
Al Nielsen / Jeff Dawson \ Tim Leighton
Margaret Rice
Debbie Smegal
Jim Tompkins
Don Stubbs
Kathleen Martin

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TOXIC SUBSTANCES

MEMORANDUM

DATE: 24 NOV 98

SUBJECT: PP#5E04526. Difenoconazole (CGA-169374 Sico® 259 EC Fungicide) in/on Imported Bananas and PP#2F4107. Difenoconazole (**Dividend®**) in/on Wheat and Animal RACs. **HED Risk Assessment**. PC Code: 128847. Barcode: D234002 and D250092. Case 283543 and 286648.

FROM: Dana Vogel, Chemist
Susie Chun, Chemist
Albin Kocialski, Ph.D, Toxicologist
RAB1/ HED (7509C)

THROUGH: Melba Morrow, D.V.M., Branch Senior Scientist
RAB1/HED (7509C)

TO: Cynthia Giles-Parker/John Bazuin (PM Team 22)
Registration Division (7505C)

Novartis has proposed tolerances for residues of the fungicide difenoconazole ([(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1*H*-1,2,4-triazole) in/on imported bananas. The proposed import banana tolerance, expressed as parent compound only, is 0.2 ppm.

Time-limited tolerances are established for residues of the fungicide difenoconazole on wheat and animal RACs, as a result of seed treatment. These tolerances with an **expiration date of 12/31/98** are as follows (40 §CFR 180.475):

Wheat Grain	0.1 ppm	Wheat Forage	0.1 ppm
Wheat Straw	0.1 ppm	Milk	0.01 ppm
Eggs	0.05 ppm	Fat*	0.05 ppm
Meat*	0.05 ppm	Meat By-Products*	0.05 ppm

*of cattle, goats, horses, hogs, poultry, and sheep

A summary of the findings and an assessment of human risk resulting from the proposed and time-limited uses for difenoconazole are provided in this document. This risk assessment is being developed to determine whether current time-limited tolerances can be converted to permanent tolerances and to support the establishment of new tolerances. The hazard assessment was provided by Albin Kocialski of Registration Action Branch 1 (RAB1), the product and residue chemistry data review by and dietary risk assessment by Susie Chun of RAB1, the occupational/residential risk

assessment by Dana Vogel of RAB1, and the water exposure assessment by James Hetrick of the Environmental Fate & Effects Division (EFED).

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I. EXECUTIVE SUMMARY

HED is conducting a risk assessment for difenoconazole in support of the establishment of permanent tolerances on wheat and imported bananas. The import tolerance on bananas is a new use, while the uses for wheat and animal RACs are currently registered in the U.S. with time-limited tolerances, expiring 12/31/98. HED has evaluated toxicology and residue data for difenoconazole submitted by Novartis Corporation. **The data are adequate to support a Section 3 registration and the establishment of permanent tolerances in wheat and animal commodities and import tolerances on bananas.**

Difenoconazole is a systemic fungicide. It can be used foliarly or as a seed treatment. It is effective on ascomycetes, basidiomycetes, and deuteromycetes diseases on wheat, rye, barley, and tropical crops. For the purposes of this action, liquid flowable concentrate and solid emulsifiable concentrate formulations are being considered.

The flowable concentrate is applied in a slurry of water, utilizing a mist-type application. This formulation is used as a seed treatment.. The active ingredient difenoconazole is effective for the control of several seed and soil-borne fungi (common bunt, dwarf bunt, loose smut, flag smut, seed-borne septoria, fall season powdery mildew, septoria leaf blotch and rust, and for partial control of fusarium root and crown rot and common foot rot.) in grain seeds, such as wheat, barley, cotton, and sweet corn seed.

The emulsifiable concentrate is applied in an emulsion of oil. For this petition, this formulation is the technical product used as a foliar treatment on imported bananas. It is currently registered for use in Belize with pending tolerances in Central America, Colombia, Equador, and Mexico. Difenoconazole is also registered for use on imported barley and rye.

Novartis currently has several registered labels for different formulations of Dividend. These include Dividend (EPA reg.# 100-739), Dividend (100-740), Dividend 0.15 FS (EPA reg.# 100-777), Dividend 0.31 FS (EPA reg.# 100-778), Dividend MG (EPA reg.# 100-779), Dividend WS (EPA reg.# 100-814), Dividend XL (EPA reg.# 100-885), and Dividend XL RTA (EPA reg.# 100-885). Dividend (EPA reg.# 100-739) and Dividend MG (EPA reg.# 100-779) are technical products pertaining to formulations into end-use fungicides. Dividend XL and XL RTA are mixtures of difenoconazole with other fungicides. Some of these labels indicate special formulation for on-farm use (EPA reg.#s 100-777, 100-778, 100-885). None of the labels have residential uses.

There are two products for this petition, one for wheat seed (EPA reg. # 100-740) and one for the technical product (EPA reg. # 100-739). The label for Dividend™ (EPA reg.# 100-740) is strictly for commercial seed treatment and contains the highest amount of active ingredient applied. Therefore, this label was used to develop the occupational exposure estimates.

Hazard Assessment

The toxicological data base for difenoconazole is adequate to support a Section 3 registration.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not considered to be an eye and skin irritant and is not a sensitizer.

Subchronic studies in mice and rats manifested decreased body weights, decreased body weight gains and effects on the liver at **200** ppm (mg/kg/day) and higher. Microscopic examination of the eyes of dogs at 3000 ppm (mg/kg/day) revealed unilateral and bilateral lenticular cataracts in both sexes of animals. Decreased body weights, body weight gains, and food consumption was reported in a 21 day rabbit dermal study at the LOAEL (Lowest Observable Adverse Effect Level) of **100** mg/kg/day.

Chronic studies in rats revealed decreased body weight gains and increased liver weights along with hepatocellular hypertrophy. Clinical chemistry data supported the liver pathology data suggesting that the liver was the was the primary target organ. There were no treatment related neoplastic effects. The LOAEL was **500** ppm (equal to 24.12 and 32.79 mg/kg/day for males and females respectively) and the NOAEL (No Observable Adverse Effect Level) was **20** ppm (equal to 0.96 and 1.27 mg/kg/day for males and females respectively).

Chronic feeding studies in mice showed decreased body weight gains in male and female mice at termination. Treatment related non-neoplastic lesions were confined to the liver and were supported by the clinical chemistry data at a level of 300 ppm (46.29 and 57.79 mg/kg/day for males and females respectively). Liver tumors were observed in mice at 300 ppm and higher. However, based on the excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two week due to excessive toxicity resulting in moribundity and death) and the absence of tumors at the two lower doses of 10 and 30 ppm, and the absence of genotoxicity data, the Cancer Peer Review Committee (CPRC) (Memo, Jess Rowland and Esther , 7/27/94) recommended a MOE approach in risk assessment utilizing the NOAEL of **30** ppm (**4.7** and **5.6** mg/kg/day in males and females respectively) and the LOAEL of **300** ppm (**46.3** and **57.8** mg/kg/day in males and females respectively) from the mouse study using only those biological endpoints which were related to tumor development (i.e. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis).

The CPRC classified difenoconazole as a Group C carcinogen (**possible human carcinogen**) and recommended for a margin-of-exposure (MOE) approach. The decision to classify difenoconazole as a Group C carcinogen was based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas and carcinomas in both sexes of CD-1 mice, only at doses that were considered to be excessively high for carcinogenicity testing. The MOE approach was selected because there was only very weak (limited) evidence of carcinogenic potential at doses levels not considered to be excessive, with significant changes observed only at excessive doses. In addition there was no evidence of genotoxicity. Therefore, a threshold model was selected for the estimation of risk. Although both rats and mice showed adverse effects in the liver, the MOE will be calculated from the NOAEL/LOAEL established in the mouse study, since a positive (cancer) response was seen in this species. Therefore, it was determined that a NOAEL of **4.7** mg/kg/day and a LOAEL of **46.3** mg/kg/day would be used in the calculations. The selection of a NOAEL for calculating utilizes only those biological endpoints which are related to tumor development (non-neoplastic hepatic lesions). The endpoints considered included: liver tumors, hepatocellular hypertrophy, necrosis, fatty changes,

bile stasis in mice, and hepatocellular hypertrophy in rats.

Chronic studies in dogs revealed decreased body weight gains through out the study at 500 ppm and increased levels of alkaline phosphatase at 1500 ppm. (51.2 and 44.3 mg/kg/day for males and females respectively) The LOAEL was **500** ppm (equal to **16.4** and **19.4** mg/kg/day for males and females respectively) and the NOAEL was **100** ppm.(equal to **3.4** and **3.7** mg/kg/day for males and females respectively).

The results of the 2-generation reproduction and developmental studies indicate that difenoconazole is not a reproductive or developmental toxicant.

Neurotoxicity studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds

Mutagenicity studies indicated that difenoconazole was not mutagenic under the test conditions.

Metabolism studies indicated that at high doses biotransformation from parent to metabolites were inhibited due to saturation of metabolic pathways. Primary elimination of the compound occurred via the feces with a lesser amount in the urine. The distribution of the chemical was not sex dependent and bioaccumalation was not observed.

On September 8, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of difenoconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). The FQPA Safety Factor Committee met on 10/19/98 and addressed the potential enhanced sensitivity to infants and children as required by FQPA and recommended for removal of the 10x FQPA Safety Factor.

Dose Assessment

For the acute dietary exposure and risk assessment an acute dietary RfD of **0.25** mg/kg/day was established for females 13+ years old. This selection was based on developmental effects in rabbits at the LOAEL of **75** mg/kg/day. The NOAEL was determined to be **25** mg/kg/day. There was no acute dietary RfD selected for the general population including infants and children as there were no effects observed in oral toxicology studies that could be attributable to a single oral dose.

For chronic dietary exposure and risk assessment, the chronic RfD was established based on a combined chronic/toxicity/carcinogenicity study in rats. The NOAEL of **20** ppm (equal to **0.96** mg/kg/day) was based on reduction in body weight gains and hepatocellular hypertrophy at the LOAEL of **500** ppm (equal to **24.12** mg/kg/day). The chronic RfD was established at **0.01** mg/kg/day based on inter species extrapolation (10x), and the intra species variability (10x).

The HIARC determined that both short-term and intermediate-term risk assessment are required for this use. The short-term dermal exposure was based on the rabbit developmental study even though a 21-day dermal study was available. As reproductive/fetal parameters are not evaluated in the dermal toxicity study, the consequences of these effects can not be ascertained for the dermal route of exposure. A 2-generation reproduction study was selected for intermediate-term dermal exposure. The HIARC determined that the effects seen in this study are of concern since these effects are not evaluated in the 21-day dermal study and is therefore appropriate for risk assessment. Since an oral toxicity study was selected for both short- and intermediate-term dermal exposure and risk analysis, a dermal absorption factor of **75%** should be used in the calculation of the dermal risk assessment. A long-term dermal exposure is not required based on a one time application as a seed treatment for use. However, since difenoconazole is classified a Group C carcinogen a risk calculation using the MOE approach is required for this use.

The HIARC determined that a risk assessment for non-cancer endpoint by way of inhalation exposure (any time period) is not required based on the low acute toxicity, low application rates, application method, and a one time application for seed treatment.

Dietary Risk Estimates from Food Sources

Chronic Dietary Risk (TMRC)

The RfD used for the chronic dietary analysis for difenoconazole is **0.01** mg/kg bwt/day. A chronic dietary exposure analysis was performed [DEEM™ software, USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII)] using tolerance level residues and 100 percent crop treated to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 28 subgroups. The TMRC for the all population subgroups was less than 14% for all populations. Since this is a highly conservative risk estimate, as no refinements for percent crop treated or anticipated residues were made. HED does not expect chronic dietary risk to exceed the Agency's level of concern.

Acute Dietary Risk

The HIARC recommended an acute dietary endpoint for females 13+ years old. The acute dietary exposure for the subgroup females 13+ years old represents less than 1% of the RfD. This is a highly conservative risk estimate, with tolerance level residues and 100% crop treated. A dose and endpoint were not selected for the general population and infants and children because there were no effects observed in the oral toxicological studies including maternal toxicity and developmental toxicity studies in rats and rabbits attributable to a single-dose. These values are below HED's level of concern.

Cancer Dietary Risk

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), the CPRC classified difenoconazole as a **possible human carcinogen.** The Committee recommended use of a margin-of-exposure (MOE) non-linear approach for

human risk characterization. The dietary cancer MOE is determined to be **8400**. Since the calculated cancer MOE is well above 100, the cancer risk does not exceed HED's level of concern.

Dietary Risk Estimates from Drinking Water Sources

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

Tier I estimated environmental concentrations (EEC) were calculated for both surface water (GEENEC model) and ground water (SCI-GROW). Tier I models represent the most conservative estimates of potential residues in drinking water. The drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since difenoconazole is used solely as a fungicide on the seed coat of small grains to control soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. These modeling assumptions are expected to yield highly conservative estimates for difenoconazole concentrations in drinking water. DWLOCs for acute, chronic (non-cancer), and cancer dietary risk from drinking water were calculated. Estimated environmental concentrations (EECs) from EFED for both surface and ground water did not exceed the chronic and acute DWLOCs.

Occupational and Residential Risk Estimates

HED does not currently perform exposure assessment for imported crops. Therefore, an occupational exposure assessment related to foliar treatment of imported bananas was not performed. This exposure assessment only deals with the commercial wheat seed treatment scenario and resulting exposures from treated seed.

Based on the wheat uses of difenoconazole the potential for occupational exposures exists. No potential for residential exposure exists. For this action, occupational exposure to difenoconazole is limited to the workers involved in the commercial seed treatment use. The corresponding label (EPA reg. # 100-740) strictly prohibits the use of this product at the farm site. All seed treatment with difenoconazole will be done indoors at a seed treatment facility.

In the agricultural setting, wheat planting usually consists of three functions; mixer/loader and driver/planter. The highest amount of exposure will be for the mixer/loader scenario, opening the treated seed bags and emptying the contents into the application equipment. Therefore, agricultural worker exposure to difenoconazole is expected to be minimal.

The HIARC determined that inhalation risk assessments are not required since toxicological concerns were not identified via this route of exposures. Exposures from post-application residues of difenoconazole are not expected to pose any risks.

Only short-term dermal exposure is expected for the wheat use due to the limited number of applications per year. Exposure calculations were done for the mixer/loader scenario only because this scenario represents the highest possible risk. Risk for the planter/driver is not expected to exceed this level. All exposure estimates for the mixer/loader scenario were well below HED's level of concern. The calculated cancer risks for the commercial seed treatment operations and agricultural operations are below HED's level of concern.

Long-term exposure is not expected for use of difenoconazole on agricultural, and non-agricultural areas due to one-time application. Hence, a long-term risk assessment was not conducted.

Aggregate Risk Estimates

Aggregate risk is estimated by combining dietary (food and water) and residential exposures. There are no homeowner uses for difenoconazole. Therefore, aggregate risk estimates will be based on the exposure from food and water only for the most highly exposed population subgroups and the general population as appropriate. For difenoconazole, conservative assumptions were used to estimate risk; i.e., dietary assessment -100% crop treated and residues at tolerance levels, water-Tier 1 and maximum application rate, and non-dietary-75% dermal absorption and upper bound exposure.

HED concludes with reasonable certainty that residues of difenoconazole will not result in unacceptable levels of aggregate acute, chronic, or cancer human health risk for any subgroup of the population at this time. Based on the available data and assumptions used for acute dietary/water exposure and risk estimates, the population group estimated to be the most highly exposed to difenoconazole is females (13+). The cancer aggregate risk for the general population was calculated as an MOE of 8400. Since the Agency's level of concern is for MOEs less than 100, the cancer risk does not exceed the level of concern. OPP has calculated DWLOCs for acute exposure to difenoconazole in drinking water for the females (13+ years old, nursing) to be **7500 ppb**. For chronic (non-cancer), the DWLOCs are **330** and **97 ppb** for U.S. population and nursing infants (less than 1 year old), respectively. For cancer, the DWLOC is **1600** ppb for the U.S. population. The surface water exposures were estimates to be **0.8 ppb** for acute and chronic and **12 ppb** for groundwater.

Since there are no residential uses for difenoconazole, short- and intermediate-term aggregate risk assessments were not conducted.

II. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

1. Identification of Active Ingredients

Chemical Name: ([(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1*H*-1,2,4-triazole)

Common Name: Difenoconazole

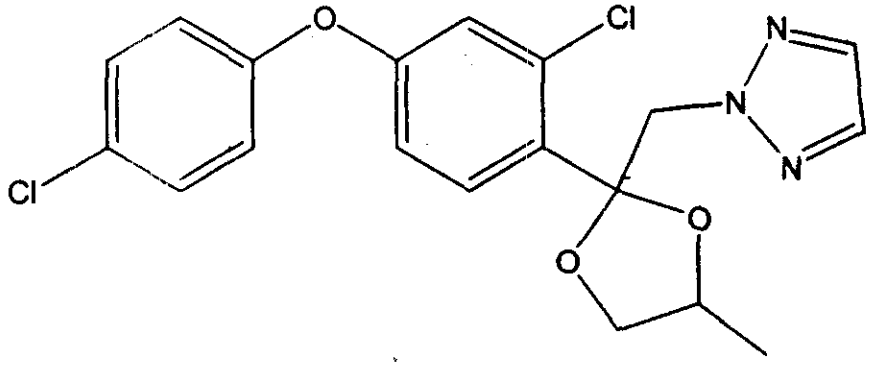
PC Code Number: 128847

CAS Registry No.: 119446-68-3

Empirical Formula: $C_{19}H_{17}Cl_2N_3O_3$

Molecular Weight: 405.06

2. Structural Formula (Difenoconazole)



3. Physical and Chemical Properties

Product chemistry data for the difenoconazole technical product were reviewed (Memo, D172067, R. Lascola, 10/26/92; Memo, G. Kramer, D194842, 3/30/94; Memo, G. Kramer, D203644, 6/16/94; Memo, G. Kramer, D210080, 1/19/95). It was concluded that the available product chemistry data was adequate to fulfill the requirements for a Section 3 permanent tolerance request. No additional product chemistry data are required for the purposes of this permanent tolerance request.

Table 1. Product Chemistry

Requirement	Results[a]	MRID Number
Color	beige -greyish	420900-03
Physical State	crystalline	420900-03
Odor	sweetish	420900-03
Melting Point	78.6°C	420900-03
Boiling Point	N/A[b]	
Density, Bulk Density or Specific Gravity	1.37 g/cm^3 typical at 20°C	420900-03

Table 1. Product Chemistry

Requirement	Results[a]	MRID Number
Solubility	Solubilities (g/100 mL at 25°C, except as noted): water: 3.3 ppm @ 20°C 1-octanol: 25 acetone: 88 ethanol: 89 *toluene*: 77 n-hexane: 0.5	420900-03
Vapor Pressure	2.5×10^{-10} mm Hg @ 25°C	420900-03
Dissociation Constant	$pK_a < 0$	420900-03
Octanol/Water Partition Coefficient	$\log K_{ow} = 4.2$ @ 25°C	420900-03
pH	6-8 typical at 20°C (saturated solution)	420900-03
Stability	Original comp.: 94.5% At 20-25°C: 6 months: 94.4% 12 months: 94.3% 24 months: 95.5% At 35°C: 3 months: 95.1% 6 months: 94.7% 12 months: 94.9% 24 months: 95.1% At 54°C: 0.5 months: 93.1% 3 months: 94.9% Stability to metals: The solid TGAI was stored in tin cans or exposed to strips of stainless steel, carbon steel and aluminum. Test samples were stored at room temperature or 38 oC. Samples were analyzed after 8, 16 and 26 weeks by visual inspection and GC analysis. No decomposition of the TGAI was observed. Stability to sunlight: The solid TGAI was exposed to simulated sunlight (Xenon arc lamp) for 24 hours. Visual inspection and chromatographic analysis demonstrated that no decomposition of the TGAI had occurred. Stability to metal ions: The TGAI was stored in 10% solutions of zinc sulfate, copper (II) sulfate, aluminum sulfate and iron (II) sulfate for 3 days at 20 or 38°C. The pH ranged from 3-4.4. The TGAI appeared to be stable in the presence of all ions except ferrous ion, in which a 3-4% decrease in difenoconazole concentration was observed.	428065-03 432365-03 434679-01
Oxidizing or Reducing Action	N/A[b]	422451-01
Flammability	N/A[b]	422451-01
Explodability	N/A[b]	422451-01
Storage Stability	N/A[b]	422451-01
Viscosity	N/A[b]	422451-01
Miscibility	N/A[b]	422451-01
Corrosion Characteristics	N/A[b]	422451-01

[a] N/A = Not Applicable.
[b] Data are not required for the TGAI.

B. Toxicology Assessment

1. Hazard Assessment

a. Acute Toxicity

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not considered to be a eye and skin irritant and is not a sensitizer. It is not neurotoxic. Table 2 and 3 summarize the toxicity studies and the categories of toxicity of this chemical.

Table 2. Acute Toxicity of Difenoconazole Technical

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	42090006	LD_{50} =1453 mg/kg	III
81-2	Acute Dermal	42090007	LD_{50} =>2010 mg/kg	III
81-3	Acute Inhalation	42090008	LC_{50} =>3300 mg/m [4 hrs. Exposure]	IV
81-4	Primary Eye Irritation	42090009	mild eye irritation reversible in 7 days	III
81-5	Primary,Skin Irritation	42090010	slight irritant	IV
81-6	Dermal Sensitization	42090011 42710004	negative	NA

b. Subchronic Toxicity

Table 3. Subchronic Toxicity of Difenoconazole

Study Type	MRID No.	Results
21-day dermal toxicity-rabbit	42090013	NOAEL=10 mg/kg/day LOAEL=100 mg/kg/day
13 week feeding mouse	42090021	NOAEL=2 mg/kg/day LOAEL=30.8 mg/kg/day
13 week feeding rat	42090022	NOAEL=1 mg/kg/day LOAEL= 37.5 mg/kg/day

Study Type	MRID No.	Results
26 week oral feeding dogs	42090012	NOAEL=31.3 mg/kg/day LOAEL=96.6 mg/kg/day
carcinogenicity study mouse	42090015; 42710006	NOAEL(systemic)=4.7 mg/kg/day LOAEL(systemic)= 46.3 mg/kg/day liver tumors in males/females
chronic toxicity/carcinogenicity in the rat	42090019;20	NOAEL=0.96 mg/kg/day LOAEL=24.12 mg/kg/day no evidence of carcinogenicity
chronic toxicity study dog	42090014; 42710005	NOAEL=3.4 mg/kg/day LOAEL=16.4 mg/kg/day
developmental toxicity rat	42090016	mater NOAEL=20 mg/kg/d LOAEL=100 mg/kg/d devel NOAEL=100 mg/kg/d LOAEL=200 mg/kg/d
developmental toxicity rabbit	42090017	mater NOAEL=25 mg/kg/d LOAEL=75 mg/kg/d devel NOAEL=25 mg/kg/d LOAEL=75 mg/kg/d
reproductive toxicity	42090018	parent NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/d offspg NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/d
gene mutation-Salmonella	42090025	non-mutagenic +/- activation
gene mutation-E.coli	42710011	non-mutagenic +/- activation
micronucleus assay	42710012	non-mutagenic
DNA repair assay	42710012	non-mutagenic +/- activation

Study Type	MRID No.	Results
metabolism rat	42090028-31; 42710013-14	Distribution,metabolism, excretion not sex dependent. 78-94% found in feces and 8-21% in urine. No accumulation. Negligible residues in tissues at 7 days. Peak absorption at 48 hrs. Saturation of metabolic pathway at high doses.

The subchronic oral studies in rats and dogs satisfy the guideline requirements.

13 week feeding study in mice (MRID# 42090021). Five groups of CD-1 (ICR) mice composed of 15 animals /sex/dose and 20 mice /sex/controls were fed dietary concentrations of either 0, 20, 200, 2500, 7500, or 1500 ppm of 94.5% pure difenoconazole for 13 weeks (equal to 0, 2, 9, 30.8, 383.6, 1125, and 2250 mg/kg/day in males and 0, 4.4, 41.5, 558.9, 1125, 2250 mg/kg/day in females). Nearly all mice fed 7500 or 15000 ppm difenoconazole died during the first week of the study. Statistical analysis of food consumption and body weight changes over the course of the study for the remaining groups showed significantly decreased body wight gain for animals receiving 2500 ppm and a significant negative trend. Compound related effects from histological examination were confined to the liver. Mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement and vacuolation in animals receiving 2500 ppm as well hepatocyte enlargement in animals given 200 ppm of compound. The LOAEL was concluded to be **200** ppm based on decreased body weight gains and liver histopathology. The NOAEL was **20** ppm (equivalent to 2.0 mg/kg in males and 4.4 mg/kg in females).

13-week feeding study in rats (MRID# 42090022). Difenoconazole (94.5%) was administered orally in feed to CRL:CD(SD) rats at dose levels of 0, 20, 200, 750, 1500 and 3000 ppm (equivalent to 0, 1, 10, 37.5, 75, and 150 mg/kg/day) for 13 weeks. There were 20 animals/sex/dose in the control group and 15 animals/sex/dose in each of the test groups. The LOAEL was **200** ppm (10 mg/kg/day) based on a 10% decrease in the body weights of females (concurrent with a negative trend for food consumption). The LOAEL in males was **750** ppm (equivalent to **37.5** mg/kg/day) based on increases in the absolute liver weights. The NOAEL was **20** ppm (equivalent to **1** mg/kg/day).

Twenty-six week oral feeding study in dogs (MRID 42090012). Difenoconazole (94.5% pure) was given in feed to five groups of pure bred beagle dogs composed of 3/animals/sex/dose in dietary concentrations of 0, 100,

1000, 3000 or 6000 ppm (equal to mean daily doses of 0, 3.4, 34.8, 110.6, and 203.7 mg/kg/day for females and 0, 3.6, 31.3, 96.6, and 157.8 mg/kg/day for males). The LOAEL was considered to be **3000** ppm based on unilateral or bilateral lenticular cataracts (microscopic examination] in all three female dogs and one of three males dogs). The NOAEL was concluded to be **1000** ppm (31.3 to 34.0 mg/kg/day).

Twenty-one day dermal toxicity study in rabbits (MRID42090013). Difenoconazole (94.4% pure) was administered topically under occlusion to three groups of New Zealand White rabbits (5/sex/dose) at daily dose of 10, 100, or 1000 mg/kg/day for six hours a day for 21 consecutive days. An additional group served as vehicle control. No animals died on study. The LOAEL was determined to be **100** mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption. The NOAEL was **10** mg/kg/day.

c. Chronic Toxicity and Carcinogenicity

The chronic and carcinogenicity studies in rats, dogs, and mice satisfy the guideline requirements for both the chronic and carcinogenicity studies.

Combined chronic toxicity and carcinogenicity study in rats (MRID42090019;20). Difenoconazole (94.5% pure) was administered in the diet to male and female Sprague-Dawley rats (80/sex/dose) for 104 weeks at dose levels of 0, 10, 20, 500, and 2500 ppm (equal to 0, 0.48, 0.96, 24.12, or 123.7 mg/kg/day in males and 0, 0.64, 1.27, 32.79, or 169.6 mg/kg/day in females) for 104 weeks. Body weight gains were reduced in groups receiving 500 and 2500 ppm of test compound. Mean liver weights were increased at week 53 and at termination in animals given 2500 ppm. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm group at termination. Clinical chemistry data supported the pathology data in that the liver was the primary target organ. There were no treatment related increased incidences of neoplastic findings observed in this study. The LOAEL was determined to be **500** ppm equal to **24.12** mg/kg/day and **32.79** mg/kg/day for males and females respectively based on reductions in body weight gains and hepatocellular hypertrophy. The NOAEL was **20** ppm equal to **0.96** and **1.27** mg/kg/day for males and females, respectively.

Chronic toxicity study in the dog (MRID 42090014; 4271005). Forty male and female dogs were divided into five animals/sex/dose and fed dietary concentrations of either 0, 20, 100, 500 or 1500 ppm (equal to 0, 0.71, 3.4, 16.4, 51.2 mg/kg/day for males and 0, 0.63, 3.7, 19.4, and 44.3 mg/kg/day) of 94.5% difenoconazole for 52 weeks. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day seven and inhibited but not statistically significant body weight gains at 500 and 1500 ppm through out the remainder of the study. Food consumption was also sporadically decreased throughout the study. Significant increases were also noted for alkaline phosphatase in males given 1500 ppm.

There were no compound related effects associated with either gross or microscopic pathology. The LOAEL was **500** ppm based on decreased body weight gains through out the study as well as decreased food intake. The NOAEL was **100** ppm (3.4 to 3.7 mg/kg/day).

Carcinogenicity study in mice (42090015; 427100006). Groups of 60-70 male and female Crl:CD-1 mice were fed diets of difenoconazole (94.5% pure) at concentrations of either 0, 10, 30, 300, 2500, or 4500 ppm (equal to 0, 1.5, 5, 46, 423, and 819 mg/kg/day in males and 0, 2, 6, 58, and 512 mg/kg/day in females) for 78 weeks. All females receiving 4500 ppm died within the first two weeks of the study. A statistically significant increasing trend in mortality was noted for males but not for females. Food consumption was comparable between control and treated groups; however body weight gain when compared to controls for male mice at termination revealed decreases of 12, 10 and 34 percent at dose levels of 300, 2500 and 4500 ppm and in females body weight gain values were 7 and 22 percent lower when compared to controls. Alterations in clinical chemistry were manifested as elevations in alanine aminotransferase, sorbitol dehydrogenase, and serum alkaline phosphatase in males at 2500 and 4500 ppm and in females at 2500 ppm. Treatment related non-neoplastic lesions were confined to the liver at 300 ppm and above in males and females (necrosis of individual hepatocytes, focal and multi focal necrosis, hepatocellular hypertrophy, inflammation, bile stasis, and fatty changes).

Male mice had significant ($p<.01$) increasing trends in hepatocellular adenomas, carcinomas and combined adenomas and carcinomas. Pair wise comparison showed a significant ($p<.05$) increase in hepatocellular adenomas at 300 and 2500 ppm when compared to controls as well as at 2500 ppm. Pair wise comparisons also showed increases ($p<.01$) at 4500 ppm in males for adenomas, carcinomas and adenomas and carcinomas combined. Female mice had a dose related trend ($p<.01$) for adenomas, carcinomas and for combined tumors. Pair wise comparisons at 2500 ppm for females reached statistical significance for adenomas ($p<.01$), carcinomas ($p<.05$) and for tumors combined ($p<.01$). The CPRC determined (Memo, J. Rowland and Esther Rinde, 7/27/94) that the two high doses of 2500 and 4500 ppm were excessive in both sexes and also determined that there was
significant toxicity (including liver necrosis) at 300 ppm in the male mice; this dose also had a significant increase in liver adenomas. The remaining doses (10 and 30 ppm) did not have statistically significant increases in liver tumors. Since there were no doses between 300 and 2500 ppm and because of the excessive toxicity at the two highest doses the CPRC concluded that this may not have been an appropriate test. Therefore based on the increased incidence of liver tumors in both sexes of mice, by both pair wise and trend analysis, consideration of the excessive toxicity at the two high doses, the absence of genotoxicity concern, the CPRC recommended for the margin-of-exposure approach (MOE) for the quantification of human risk utilizing the NOAEL/LOAEL from the mouse study. It was therefore determined that a NOAEL of **4.7** mg/kg/day and a LOAEL of **46.3**

mg/kg/day would be used in the MOE calculations using only those biological endpoints which were related to tumor development (non-neoplastic hepatic lesions) which were hepatocellular hypertrophy, necrosis, fatty changes and bile stasis in mice (and hyper cellular hypertrophy in rats). The LOAEL is **46.3** based on hepatocellular hypertrophy, necrosis, fatty changes and bile stasis . The NOAEL was **4.7** (5.0 mg/kg/day).

d. Developmental and Reproduction Toxicity

Developmental toxicity study in rats (MRID# 42090016). Difenoconazole was administered to Crl:COBS CD (SD) pregnant rats at dose levels of 0, 2, 20, 100, or 200 mg/kg/d from days 6-15 of gestation. Statistically significant decreases in maternal body weight gain and feed consumption were observed during the dosing period at dose levels of 100 and 200 mg/kg/day. Body weight gain decreases of 21% and 57% were recorded for the 100 and the 200 mg/kg/day dose groups for days 6-15. At 200 mg/kg/day the incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on a fetal basis. There was also significant increases in the average number of ossified hyoid and decreases in the number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased with accompanying increases in the number of thoracic vertebrae and decreases in the number of lumbar vertebrae in this group. (The DER indicates that these findings at the highest dose tested of 200 mg/kg/day appear to be the result of maternal toxicity). The NOAEL for maternal toxicity was **20** mg/kg/day and the LOAEL for maternal toxicity was determined to be **100** mg/kg/day based on decreased body weight gains and decreased food consumption at 100 mg/kg/day and higher. The NOAEL for developmental toxicity was **100** mg/kg/day and the LOAEL **200** mg/kg/day based on the incidence of bifid or unilateral ossification of the thoracic vertebrae which was significantly increased in on a fetal basis, and the significant increases in the average number of ossified hyoid and decreases in the number of sternal centers of ossification (per fetus per litter). The average number of ribs was also significantly increased with accompanying increases in the number of thoracic vertebrae and decreases in the number of lumbar vertebrae in this group.

Developmental toxicity study in rabbits (MRID# 42090017). In a developmental toxicity study, impregnated rabbits (16/dose) were given oral administration of difenoconazole at 0, 1, 25, or 75 mg/kg/day during days 7 through 19 of gestation. At 75 mg/kg/day, maternal toxicity was manifested as decreased body weight gain and food consumption; no maternal toxicity was observed at lower doses. Developmental toxicity observed only at 75 mg/kg/day was a slight non-significant increase in post-implantation loss and resorption/doe and a significant decrease in fetal weight. For maternal toxicity, the LOAEL of **75** mg/kg/day is based on decreases in body weight gain and food consumption; the NOAEL is **25** mg/kg/day. For developmental toxicity, the LOAEL of **75** mg/kg/day is based on increases in post-implantation loss and resorption per doe and decreases in fetal body weight; the NOAEL is **25** mg/kg/day.

Two generation reproduction study in rats (MRID# 42090018). In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm (0, 1.25, 12.5, or 125 mg/kg/day, respectively). Statistically significant reductions in body weight gains of F_0 and F_1 males were observed at 2500 ppm during Days 70-77 and during the course of the study (terminal body weight minus Day O body weight). Significant reductions in body weight gains of F_0 and F_1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F_0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation. At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 (pre- and post culling), 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F_1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F_1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm group. For parental toxicity, the LOAEL of **250** ppm (**12.5** mg/kg/day is based on the decreased maternal body weight gain; the NOAEL is **25** ppm (**1.25** mg/kg/day). For reproductive toxicity, the LOAEL of **250** ppm (**12.5** mg/kg/day) is based on decreased pup weights at Day 21; the NOAEL is **25** ppm (**1.25** mg/kg/day).

e. Neurotoxicity

These studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

f. Mutagenicity

Mutagenicity (MRID 42090025;42710011;-12). Difenoconazole was not mutagenic with or with out metabolic activation when tested at concentrations ranging from 340 to 5447 micrograms/plate in two independently performed microbial/mammalian microsome plate incorporation assays using Salmonella typhimurium strains TA1535, TA1537, TA98, and TA 100 and Escherichia coli strain WP2uvrA. In an *in vivo* micro nucleus assay, no increase in micro nucleated polychromatic erythrocyte counts were seen in the bone marrow cells of mice given oral administration of difenoconazole at 0, 400, 800 or 1600 mg/kg/day. Difenoconazole was negative in an *in vitro* UDS assay with primary rat hepatocytes at concentrations up to 50.0 ug/ml

g. Metabolism

Metabolism (MRID 420900-28,29,30,31; 427100-13,14) Animals were administered a single oral gavage dose of 0.5 or 300 mg of ^{14}C difenoconazole or 0.5 mg/kg unlabeled difenoconazole by gavage for 14 days followed by a single

gavage dose of 0.5 mg/kg ^{14}C on day 15.The biotransformation of difenoconazole is shown in the attached flow chart (Attachment 3). The compound undergoes successive oxidation and conjugation reactions. One of the metabolites, CGA-205375, accounts for 6-24% of the applied dose and is found only in the urine and feces of high dose (300 mg/kg) rats. The presence of this intermediate in the excreta of only high dose rats, suggests that its rate of further biotransformation has reached saturation at he high dose. Additionally, excretion of radioactivity in the bile, feces, and urine of rats orally dosed with ^{14}C-difenoconazole is consistent with saturation of the gastrointestinal absorption of the chemical at 300 mg/kg. The distribution, metabolism and excretion were not sex dependent. The elimination in the feces ranged between 78 and 94 % and in the urine from 8-21%. Peak absorption occurred between 24-48 for dosing groups. The study also indicated that the compound does not accumulate to any appreciable extent since tissues contained negligible residues (<1%) of radioactivity after 7 days post-exposure.

The metabolism study in the rat is acceptable and satisfies the guideline requirement for a metabolism study (85-1) in the rat.

2. Dose Response Assessment

On September 25, 1998, the Health Effects Division's HIARC report evaluated the toxicology data base of difenoconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). The FQPA Safety Factor Committee report dated October 28, 1998 also addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The CPRC previously met on July 27, 1994 to evaluate the carcinogenic potential of difenoconazole.

a. Reference Dose (RfD)

A chronic RfD of **0.01** mg/kg/day was established, based on the NOAEL of **0.96** mg/kg/day established in the 104 week chronic toxicity/carcinogenicity in rats and using an uncertainty factor of 100 (10x for inter-species extrapolation, 10x for intra-species variability, 1X for FQPA). The LOAEL in this study, **24.12** mg/kg/day, was based on cumulative decreases in body weight gains.

b. Carcinogenicity Classification and Risk Quantification

The Health Effects Division (HED) CPRC met on May 18, 1994 to discuss and evaluate the weight of evidence on difenoconazole with particular reference to its carcinogenic potential. The CPRC concluded that difenoconazole should be classified as a Group C - **possible human carcinogen** and recommended that for the purpose of risk characterization, the margin-of-exposure (MOE) approach

should be used for the quantification of human risk (Memo, Jess Rowland and Esther Rinde, 7/27/94).

The decision to classify difenoconazole as a Group C carcinogen was based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas and carcinomas in both sexes of CD-1 mice, only at doses that were considered to be excessively high for carcinogenicity testing. The MOE approach was selected because there was only very weak (limited) evidence of carcinogenic potential at doses levels not considered to be excessive, with significant changes observed only at excessive doses. In addition there was no evidence of genotoxicity. Therefore a threshold model was selected for the estimation of risk. Although both rats and mice showed adverse effects in the liver, the MOE will be calculated from the NOAEL/LOAEL established in the mouse study, since a positive (cancer) response was seen in this species. Therefore, it was determined that a NOAEL of **4.7** mg/kg/day and a LOAEL of **46.3** mg/kg/day would be used in the calculations. The selection of an NOAEL for calculating utilizes only those biological endpoints which are related to tumor development (non-neoplastic hepatic lesions). The endpoints considered included: liver tumors, hepatocellular hypertrophy, necrosis, fatty changes, bile stasis in mice, and hepatocellular hypertrophy in rats. In addition, those doses levels represented the majority of the NOAELs and LOAELs for the endpoints examined. Most of the other NOAELs, and LOAELs were higher than the one selected.

c. Other Toxicological Endpoints

i. Acute Dietary

A dose and endpoint was selected for the population subgroup females 13+ years old for dietary risk assessment because there were effects that were attributable to a single dose (exposure) observed in rabbit developmental studies. There were increases in post-implantation loss and resorption which are presumed to occur after a single exposure and was therefore considered appropriate for this risk assessment since these are *in utero* effects. The dose and endpoint selected for this population subgroup was **25** mg/kg/day (NOAEL) based on post-implantation loss and resorption per doe and a significant decrease in fetal weight at **75** mg/kg/day which was the LOAEL. The acute RfD was determined to be **0.25** mg/kg/day after utilizing a **100** fold uncertainty factor.

A dose and endpoint were not selected for the general population and infants and children as there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that were attributable to a single exposure (dose).

ii. Occupational/Residential Exposure

a) Dermal Absorption

A dermal absorption study is not available. Therefore, the HIARC estimated a dermal absorption factor based on the LOAEL established for the same endpoint in the oral developmental toxicity study in rabbits and the 21-day dermal toxicity study in rabbits. In the oral developmental toxicity study in rabbits, the maternal LOAEL was **75** mg/kg/day based on the decreased body weight gain and food consumption; the maternal NOAEL was **25** mg/kg/day (MRID# 42090017). In the 21-day dermal toxicity study in rabbits, the systemic toxicity LOAEL was **100** mg/kg/day based on decreases in body weight, body weight gain and food consumption; the NOAEL was **10** mg/kg/day (MRID# 420900-13).

The ratio of the LOAELs from the oral and dermal studies indicated an approximate dermal absorption rate of **75%** (75÷100=75%).

Dermal absorption factor = **75%**

b) Short-Term (1-7 Days) Dermal

A developmental rabbit study was selected for a short term dermal exposure. A 21-day dermal study in rabbits is available, however a developmental study was selected because: 1) the endpoint in the 21-day study was limited to changes in body weights and food consumption; 2) developmental effects were considered to be appropriate for this exposure period of concern (1-7 days); 3) reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects can not be ascertained for the dermal route of exposure; and 4) the endpoint will provide adequate protection for the subpopulation female 13+ (i.e. pregnant workers). Since an oral NOAEL was selected a dermal absorption factor of 75% should be used for this dermal risk assessment. NOAEL = **25** mg/kg/day based on post-implantation loss and resorption/dose and a significant decrease in fetal weight at **75** mg/kg/day (LOAEL). This risk assessment is required.

c) Intermediate-Term (7 days to several months) Dermal

A two generation reproduction study was selected for a short term dermal l exposure. A 21-day dermal study in rabbits is available, however a reproduction study was selected because: 1) the endpoint in the 21-day study was limited to changes in body weights and food consumption; 2) reproductive effects were considered to be appropriate for this exposure period of concern (7 days to several months); 3) reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects can not be ascertained

for the dermal route of exposure. Since an oral NOAEL was selected a dermal absorption factor of 75% should be used for this dermal risk assessment. The NOAEL was determined to be **1.25** mg/kg/day based on decreased pup weight at **12.5** mg/kg/day (LOAEL) on day 21. This risk assessment is required.

d) Long-Term (several months to life) Dermal

Long term dermal exposure is not expected based on a one time application as a seed treatment to wheat. This risk assessment is not required for a long term non-cancer dermal (end point) effects. Difenoconazole is however classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (Memo, Jess Rowland and Esther Rinde, 7/27/94) Although both rats and mice showed adverse effects in the liver, the MOE will be calculated from the NOAEL/LOAEL established in the mouse study, since a positive (cancer) response was seen in this species. Therefore, it was determined that a NOAEL of **4.7** mg/kg/day and a LOAEL of **46.3** mg/kg/day would be used in the calculations. The selection of an NOAEL for calculating the MOE utilizes only those biological endpoints which are related to tumor development (non-neoplastic hepatic lesions). The endpoints considered included: hepatocellular hypertrophy, necrosis, fatty changes, bile stasis in mice, and hepatocellular hypertrophy in rats .A dermal absorption factor of **75%** should be used for route-to-route extrapolation.

e) Inhalation Exposure (Any-Time period)

This risk assessment is not required for non-cancer endpoint as there is minimal concern for potential inhalation exposure/risk. This is based on the low acute toxicity of the chemical (Toxicity Category IV) , the application rate (**0.5-1.0 fl. oz./100** lbs of seed) the application method (standard slurry or mist-type seed treater) and the number of applications (1x). This risk assessment is required for the endpoint of cancer (Memo, A. Kocialski and Jess Rowland, 9/25/98).

3. **FQPA *Considerations***

a. Neurotoxicity Data

These studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

b. Determination of Susceptibility

Acceptable prenatal toxicity studies in rats and rabbits with difenoconazole have been submitted to the Agency. An acceptable reproductive toxicity study in rats with difenoconazole was also available. Hence, there were no data gaps for the assessment of the effects of difenoconazole following *in utero* exposure or the effects on young animals following early exposure. The data provided no indication of increased susceptibility of rats or rabbits to *in utero* or post-natal exposure to difenoconazole. See preceding executive summaries for the relevant findings from the developmental toxicity and reproductive toxicity studies.

c. Recommendation for a Developmental Neurotoxicity Study

The HIARC determined that a developmental neurotoxicity study in rats is not required based on the following factors:

- Difenoconazole is not structurally related to a neurotoxic agent.
- There is no evidence in the acute, subchronic or the chronic studies that difenoconazole induces neurotoxic effects.
- No increased susceptibility was seen in the prenatal developmental toxicity studies and in the pre/post natal reproductive toxicity study
- There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

d. Determination of the FQPA Factor

HED's FQPA Safety Factor Committee met on October 19,1998 (Memo, B. Tarplee, 10/28/98) to evaluate the hazard and exposure data for difenoconazole and recommend application of the FQPA Safety Factor (as required by FQPA of August, 1996), to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be removed and replaced with a 1x factor.

The Rationale for Selection of the 1x FQPA Factor was:

A) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits;

B) The two generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults; and

C) There was no evidence of abnormalities in the development of fetal

nervous system in the pre/post natal studies. Neither brain weight nor histopathology (perfused or nonperfused) of the nervous system was affected in the subchronic and chronic toxicity studies.

D) The toxicology data base is complete and there are no data gaps.

4. Data Gaps

There are no data gaps.

5. Summary of Toxicology Endpoint Selection

The doses and toxicological endpoints selected on difenoconazole for various exposure scenarios are summarized in Table 4.

Table 4. Summary of Toxicological Endpoints of Difenoconazole

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary [females 13+]	NOAEL= 25 UF = 100	post-implantation loss, increased resorption per doe, decreased body weight	developmental rabbit
	Acute RfD = 0.25 mg/kg		
Acute Dietary (General Population including infants and children)	None	An endpoint attributable to a single exposure (dose) was not available from the oral toxicity studies including the rat and rabbit developmental toxicity studies.	
Chronic Dietary	NOAEL = 0.96	cumulative decreases in body weight gains	chronic/one rat
	UF = 100	**Chronic RfD = 0.01 mg/kg/day**	
Short-Term[a] (Dermal)	oral NOAEL=25	post-implantation loss, increased resorption per dose, decreased body weight	developmental rabbit
Intermediate-Term[a] (Dermal)	oral NOAEL=1.25	based on decreased pup weight on day 21	2-generation reproduction rat
Long-Term (Dermal)[a] Non Cancer	None	Long-term dermal exposure is not expected based on a one time application as a seed treatment. This risk assessment is not required.	

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Long-Term Dermal[a] (Cancer)	NOAEL =4.7	Difenoconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94).	
Inhalation (Any time period)	None	Based on the low acute toxicity [Toxicity_Category IV] , the application rate [0.5-1.0 fl.oz./100 lbs of seed] the application method [standard slurry or mist-type seed treater] and the number of applications [1x] there is minimal concern for potential inhalation exposure/risk. This risk assessment is not required for the non-cancer endpoint.	

a =A dermal absorption factor of 75% should be used for route-to-route extrapolation.

6. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Sources)

i. Proposed Uses

Wheat

Dividend is a flowable concentrate of difenoconazole containing 3 lbs. ai/gal. Dividend is applied as a water-based slurry by mixing with up to 16 oz. water per 100 lbs. seed. The maximum use rate is 1 fluid oz./100 lbs. seed (10.9 grams or 0.38 oz./100 lbs. seed). The label contains the following restrictions: a) do not use treated seed for feed, food or oil; b) green forage may not be grazed until 55 days after planting; c) do not apply to winter barley; d) for use only by commercial seed treaters (Memo, G. Kramer, D194842, 3/30/94). The data submitted support a 30-day plantback interval for all rotational crops (Memo, G. Kramer, D217119, 9/13/95).

Bananas

Difenoconazole (EPA Reg. No. 100-739) is formulated as Sico 25EC, a emulsifiable concentrate containing 23.9% a.i. A CSF was included for Sico. Sico is currently registered for use on bananas in Belize. Registrations are pending in Central America (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama and the Dominican Republic), Colombia, Ecuador and Mexico. Labels and English translations were provided for all of these regions/countries (Memo, G. Kramer, D216521, 2/23/96).

The maximum use rate is 40.5 g. ai/A (100 g. ai/ha) and a maximum of 12 applications are permitted per year. The minimum re-treatment interval is 18 days. A maximum of 8 applications are recommended when the 18-day re-

treatment interval is utilized (Memo, G. Kramer, D216521, 2/23/96).

Difenoconazole can be applied as an emulsion, or in oil only. The emulsion is prepared by mixing 5-10 L oil with 15-20 L water plus 0.5-1.0% emulsifier for each liter of oil. The application volumes are 99-205 l/ha for concentrated applications and 20-25 l/ha for ULV applications. These directions are applicable to both ground and aerial applications. The PHI is 0 days (Memo, G. Kramer, D229926, 10/4/96).

ii. Nature of the Residue - Plants

Wheat

The nature of the residue in wheat is understood. Acceptable metabolism studies using [^{14}C]- labeled difenoconazole have been performed in wheat RACs. Difenoconazole was applied in phenyl- and triazole-labeled forms. The major terminal residues in wheat grain are the metabolites triazole and triazole acetic acid; and in wheat straw and forage; triazole alanine, triazole acetic acid and CGA-205375. The parent was not detected in grain and comprised 7-8% of the TRR in forage and 0.3-0.4% of the TRR in straw (Memo, G. Kramer, D203644, 6/16/94).

Bananas

The nature of the residue is understood in tomatoes, potatoes, wheat (PP#2E4051), and grapes (Memo, G. Kramer, D216521, 2/23/96).

The nature of the residue in **tomatoes** following foliar application is adequately understood. The major terminal residues are the parent compound and its metabolite triazole alanine, (CGA-131013). (Memo, R. Lascola, D172067, 10/26/92).

The petitioner has established that the primary metabolic fate of difenoconazole in **potatoes** following foliar application is cleavage of the phenyl-triazole bridge. Triazole-labeling studies indicate that the molecule is metabolized to triazole alanine, while phenyl studies demonstrate conjugating with a number of naturally occurring substrates (Memo, R. Lascola, D172067, 10/26/92).

The nature of the residue in **grapes** is understood. The metabolism of difenoconazole proceeds by hydroxylation of the phenyl ring and/or oxidative cleavage of the dioxolane ring followed by cleavage of the carbon-carbon bridge between the phenyl and triazole rings. Similar results were observed in the wheat, tomato and potato metabolism studies (Memo, G. Kramer, D216521, 2/23/96).

The nature of the residue in plants is believed to be understood. As the nature of the residue is understood in different crops, no metabolism studies for bananas were required.

The residue of concern in bananas is the parent compound only (Memo, G. Kramer, D216521, 2/23/96).

The HED Metabolism Assessment Review Committee (MARC) met on July 14, 1994 to discuss the toxicological significance of potential metabolites. It was decided that none of the difenoconazole metabolites warrant inclusion in the tolerance regulation or separate regulation or inclusion in the dietary risk assessment or additional metabolism or toxicological studies. The triazole metabolites (triazole, triazole alanine, triazole acetic acid) have previously been determined not to be of toxicological concern in conjunction with tebuconazole. CGA-205375 was determined not to be of concern due to the low potential for residues associated with seed treatment (Memo, G. Kramer, 7/22/94). This conclusion can be expanded to include triazole propanoic acid (Alberto Protzel, Personal Communication 1/17/95) (Memo, Kramer, D210080, 1/18/95).

However, if in the future the registrant wishes to propose tolerances for difenoconazole resulting from foliar uses which result in higher residue levels, then the MARC will reconsider whether CGA-205375 needs to be included in the difenoconazole tolerance expression. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in animal feed items, then animal feeding studies will be required (Memo, G. Kramer, 7/22/94).

iii. Nature of the Residue - Animals

The nature of the residue in animals is considered understood for the purposes of this petition (2F4107) **only** (Memo, G. Kramer, D233644, 6/16/94). For any future petition in which there is a greater potential for transfer of residues to meat and milk, additional animal metabolism studies will be required.

The HED MARC met on July 14, 1994 to discuss the toxicological significance of potential metabolites. It was decided that none of the difenoconazole metabolites warrant inclusion in the tolerance regulation or separate regulation or inclusion in the dietary risk assessment or additional metabolism or toxicological studies. The triazole metabolites (triazole, triazole alanine, triazole acetic acid) have previously been determined not to be of toxicological concern in conjunction with tebuconazole. CGA-205375 was determined not to be of concern due to the low potential for residues associated with seed treatment (Memo, G. Kramer, 7/22/94). This conclusion can be expanded to include triazole propanoic acid (Alberto Protzel, Personal

Communication 1/17/95) (Memo, Kramer, D210080, 1/18/95).

However, if in the future the registrant wishes to propose tolerances for difenoconazole resulting from foliar uses which result in higher residue levels, then the MARC will reconsider whether CGA-205375 needs to be included in the difenoconazole tolerance expression. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in animal feed items, then animal feeding studies will be required (Memo, G. Kramer, 7/22/94).

iv. Residue Analytical Methods

Plants

The petitioner has proposed Method AG-575B, "Analytical Method for the Determination of CGA-169374 in Wheat Raw Agricultural Commodities by Gas Chromatography with Nitrogen/Phosphorus Detection." as the analytical enforcement method for wheat (Memo, R. Lascola, D172067, 10/22/92) and bananas (Memo, G. Kramer, D216521, 2/23/96).

Frozen samples are homogenized, and residues are extracted by boiling the samples in 8:2 methanol:concentrated ammonium hydroxide solution. The extract is diluted in water and partitioned twice with hexane. The organic layer is then partitioned twice with acetonitrile (ACN). The residues are now in the ACN phase. The ACN is evaporated and redissolved in toluene for cleanup on a silica Sep-Pak column. The toluene is evaporated, the residue dissolved in hexane, and a second cleanup is performed on a phenyl Bond-elut column. A third cleanup is then performed with a charcoal column, with toluene as the solvent. Detection is achieved by GC with a nitrogen/phosphorus detector. The petitioner notes that it may be necessary to increase the N/P element power in order to obtain sufficient peak height of the lowest calibration standard. A set of 4-6 samples can be extracted, cleaned up, and analyzed in "a 24 hour period." The method does not require use of an untreated commodity or a blank (Memo, R. Lascola, D172067, 10/22/92).

The petitioner has submitted a confirmatory method (AG-657, MRID# 440933-01). This method differs from the enforcement method in the GC column and detector used (DB-1701/ECD instead of DB-17/NPD). In bananas fortified at 0.01-0.20 ppm, the average recovery was 106 ± 14% with the enforcement method and 99 ± 13% with the confirmatory procedure. Conditions for using MSD (monitoring m/z 323 and 265) were also included (Memo, G. Kramer, D229926, 10/4/96).

HED concluded that Method AG-575B is adequate for enforcement purposes. An independent laboratory validation (ILV) of the method has been submitted

and a satisfactory petition method validation (PMV) by ACL has been completed (Memo, G. Kramer, D194842, 3/30/94).

Animals

The petitioner has proposed Method AG-544A, "Difenoconazole (CGA-169374) Analytical Method for the Determination of CGA-169374 Residues in Dairy and Poultry Tissue, Eggs and Milk by Gas Chromatography," as the analytical enforcement method. The sample is extracted by homogenization for 1 min with 95:5 acetonitrile:concentrated ammonium hydroxide. After filtration, the extract is diluted with water and saturated NaCl and partitioned with hexane. The hexane fraction is partitioned with acetonitrile and the acetonitrile fraction is cleaned-up on a silica gel SepPak. The final extract is analyzed by packed column GC using alkali flame ionization detection (Memo, G. Kramer, D194842, 3/30/94).

HED concludes that Method AG-544A is adequate for enforcement purposes. An ILV of the method has been submitted and a satisfactory PMV by ACL has been completed (Memo, G. Kramer, D205118, 7/20/94).

v. Multiresidue Methods

The results of Multiresidue testing of difenoconazole its metabolites, CGA-189138, CGA-205374, and CGA-205375, (MRID# 420900-54) have been forwarded to FDA (Memo, R. Lascola, 5/21/92). The method is entitled "Multiresidue Method Testing of CGA-169374 and Metabolites in Crops and Animal Tissues", CIBA-GEIGY Project No. ABR-89048, by R. K. Williams, CIBA-GEIGY Corporation, Greensboro, NC; 7/20/92; MRID# 420900-54. Compounds investigated included CGA-169374, CGA-205374, CGA-205375, and CGA-189138. The petitioner concluded that Protocols C, D, and E did not yield sufficient recoveries or responses to be useful for the detection of these chemicals. Protocol A (N-methyl carbamates) does not apply to these chemicals. Protocol B (acids and phenols) only applies to CGA-189138; however, recovery of that compound was not tested (Memo, R. Lascola, D172067, 10/22/92).

vi. Storage Stability Data

Wheat

The petitioner has submitted acceptable storage stability data in wheat grain, straw, and forage and in cottonseed, cottonseed oil, and cottonseed meal. The data shows difenoconazole to be stable for up to 24 months frozen storage. HED concludes that storage stability has been demonstrated for the purposes of this petition (Memo, S. Chun, D248285, 10/28/98).

Bananas

These results demonstrate that residues of difenoconazole are stable in bananas for up to 12 months of storage. Difenoconazole has been previously shown to be stable in potatoes and tomatoes for up to 2 years of storage and in wheat for 1 year (Memos, R. Lascola, D172067, 10/22/92 and G. Kramer, D194842, 3/30/94). Based on submitted studies, storage stability is not an issue for this petition. (Memo, G. Kramer, D216521, 2/23/96).

vii. Crop Field Trials

Wheat

Fifteen field trials were conducted in OK (2), TX (1), NC (1), MT (1), KS (2), CO (1), ND (1), SD (1), AR (1), ID (1), MO (1), MN (1), and NE (1). This corresponds to the following regions: Region 2 (1 trial), Region 4 (1 trial), Region 5 (3 trials), Region 7 (2 trials), Region 8 (6 trials), and Region 9 (2 trials). The number of field trials in each region do not match those suggested in *Residue Chemistry Test Guidelines, OPPTS 860.1500 Crop Field Trials.* A field trial in region 6, 2 field trials in region 7, and a field trial in region 11 are missing; however, the submitted field trials accounted for 83% of total wheat acreage planted. Therefore, no additional field trials in these regions will be required. The wheat field trials were conducted at two application rates, 10.9 g a.i./100 lb. seed (1x) and 21.8 g a.i./100 lb. seed (2x). At each site wheat grain, forage, hay, and straw were collected. Two samples were collected per plot for the 1x application.

The submitted field trial data on wheat RACs are adequate. The average method recoveries for the field trials were acceptable (> 70%) for wheat RACs. The residue levels of difenoconazole in wheat grain (< 0.01 ppm) and in wheat hay and straw (< 0.05 ppm) were less than the limit of quantitation (LOQ). Wheat forage had residue levels ranging from < 0.05 ppm - 0.077 ppm. The submitted data indicate that residues of difenoconazole will not exceed the time-limited tolerance for wheat RACs (Memo, S. Chun, D48285, 10/28/98).

Bananas

Nine field trials were conducted in Colombia (3), Honduras (3), and Ecuador (3). Two of three field trials in each country were conducted using an oil emulsion at the single maximum application rate of 100 g a.i./ha (0.22 lb. a.i./ ha); one using aerial application and one using ground application. Difenoconazole was applied 8 times for a total maximum application rate of 800 g a.i./ha (1.76 lb. a.i./ha) with a target spray volume range of 20-25 L/ha/application. The third field trial used an oil only formulation at an application rate of 100 g a.i./ha (0.22 lb. a.i./ha) and was also applied 8 times

for a maximum application rate of 800 g a.i./ha (1.76 lb. a.i./ha) using aerial application with a target spray volume of 10 L/ha/application. At each site whole banana fruit were collected 0 days after the last application. Specimens were collected from unbagged racemes (bunches) in all field trials. Samples consisted of six fingers (two fingers from top, middle, and bottom hands of a raceme). A total of six replicates were collected (each using another plant raceme) for each treatment. The studies were conducted in accordance with the protocol submitted to and accepted by HED (Memo, G. Kramer, D227491, 8/1/96). The varieties of bananas used in these field trials were: AAA, Cavendish, Robusta, Valery, and Giant Cavendish. The submitted 9 field trial data in bananas are adequate. The residue levels of difenoconazole in whole bananas ranged from <0.02 ppm to 0.13 ppm. The residue levels in banana pulp were all less than the LOQ (0.02 ppm). The residue levels in banana peel ranged from < 0.02 - 0.25 ppm.

An additional six field trials were submitted and reviewed previously (Memos, G. Kramer, D216521 and D229926, 2/23/96 and 10/4/96, respectively). These field trials were conducted in Costa Rica (1 trial), Ecuador (1 trial), Mexico (2 trials), Guatemala (1 trial), and Belize (1 trial). Residue levels in these six field trials ranged from 0.03 -0.16 ppm in whole - unbagged bananas and < 0.02 - 0.03 ppm in unbagged banana pulp.

With the submission of 9 field trials and the 6 prior, the field trial data (15 trials) on bananas are adequate. The residue levels of difenoconazole in whole unbagged bananas from all 15 trials ranged from < 0.02 - 0.16 ppm. The residue levels in unbagged banana pulp from all field trials ranged from < 0.02 - 0.03 ppm. The submitted data indicate that residues of difenoconazole will not exceed the proposed tolerance level of 0.2 ppm for bananas (Memo, S. Chun, D248285, 11/2/98).

viii. Processed Food/Feed

Wheat

HED has previously reviewed a processing study for spring wheat which was seed-treated (2X) and also foliar-treated (10X) 28 days before harvest (Memo, R. Lascola 10/26/92). No residues (<0.01 ppm) were detected in grain or any processed fraction (Memo, G. Kramer, D194842, 3/30/94). No tolerances for the processed commodities are required for wheat.

Bananas

There are no processed commodities associated with bananas and therefore no tolerances for processed commodities are required.

ix. Meat, Milk, Poultry, Eggs

The registrant has requested (MRID# 428180-06) a waiver for animal feeding studies based on the low potential for residues in feed items and the exaggerated rates used in the animal feeding studies. Based on a diet comprised of 100% wheat RACs and residues at the level of the proposed tolerances, the maximum dietary burden for dairy cattle is estimated to be 0.30 ppm. Two metabolism studies were performed in ruminants (lactating goats)- a 10 day study with a dose rate of 4.17 ppm (14X the 0.30 ppm estimated dietary burden) and a 3 day study with a dose rate of 100 ppm (333X the 0.30 ppm estimated dietary burden). The Total Radioactive Residue (TRR) in the goat tissues can be used to estimate the expected residues in a feeding study with a dose rate of 0.30 ppm. The maximum residue observed was in liver, estimated to be at a level of 0.02 ppm from both metabolism studies. This value is 2.5X below the LOQ of the proposed analytical enforcement method (0.05 ppm). The estimated residue in milk would be 0.5 ppb, 20X below the method LOQ of 0.1 ppm.

For now, HED is willing to accept the registrants proposal to allow the animal metabolism studies to also serve as feeding studies. Feeding studies in cattle and poultry, as appropriate, will be needed for any future tolerance requested on potential livestock feed commodities which could lead to higher residues of concern in meat, milk and eggs (Memo, G. Kramer, D194842, 3/30/94).

x. **Water, Fish, and Irrigated Crops** - Not Applicable

xi. **Food Handling** - Not Applicable

xii. **Confined Accumulation in Rotational Crops**

The nature of the residue is understood. The data indicate that the phenyl/triazole bridge of difenoconazole is cleaved in the soil and that triazole-specific metabolites are preferentially taken up by the rotational crops. The maximum TRR observed with phenyl-labeled difenoconazole was 0.009 ppm (wheat stalks); with triazole-labeled difenoconazole, 0.314 ppm (wheat grain) (Memo, G. Kramer, D210080, 1/18/95).

The registrant has submitted the results of two confined crop rotation studies using phenyl-labeled difenoconazole. In the RACs of all rotational crops planted 30-33 days after application of difenoconazole, the TRR was <0.01 ppm. These results support the proposed 30 day plantback restrictions for all rotational crops (Memo, G. Kramer, D217119, 9/13/95).

xiii. **Field Accumulation in Rotational Crops** - Not Applicable

xiv. **Tolerance Reassessment Table** - Not Applicable

xv. **Anticipated Residues** - Not Applicable

xvi. **Codex Harmonization**

There are pending Codex MRL's for this compound in Mexico for oats, wheat, and barley. There are MRL's for this compound in Australia for carrots (0.5 ppm), potatoes (0.02 ppm), and bananas (0.5 ppm).

b. Dietary Exposure (Drinking Water Source)

HED and EFED do not have monitoring data available to perform a quantitative drinking water risk assessment for difenoconazole at this time. EFED provided ground and surface water exposure estimates using screening models for use of difenoconazole (parent compound only).

The drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since difenoconazole is used solely as a fungicide on the seed coat of small grains to control seed and soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. These modeling assumptions are expected to yield highly conservative estimates for difenoconazole concentrations in drinking water. In order to conduct Tier 1 modeling for difenoconazole, the following assumptions were made: 1.) Complete dissociation of difenoconazole from the seed coat is assumed; 2.) Difenoconazole is persistent ($t_{1/2}$=365 days) and mobile (K_{oc}=0.0) in terrestrial and aquatic environments; and 3.) The maximum difenoconazole application rate is 0.01498 lbs ai /A, which accounts for a maximum wheat application rate of 60 lbs seed/A treated with 11 g ai/100 kg seed. EFED recommends that the registrant submit aerobic soil metabolism and batch equilibrium data to provide a limited understanding on the fate and transport of difenoconazole. Additional environmental fate data (*e.g.*, terrestrial field dissipation) may be needed to confirm routes and rates of dissipation under actual use conditions (Memo, J. Hetrick, 10/28/98).

i. **Surface Water Estimates**

Surface water estimates were made using the GENEEC model and available fate data for difenoconazole. EFED calculated the following Tier 1 Estimated Environmental Concentrations (EECs) for difenoconazole in surface water:

Acute or peak EECs: 0.837 ppb
Chronic (56-day) EECs: 0.835 ppb

ii. **Ground Water Estimates**

Using the SCI-GROW model to estimate concentrations in ground water for the parent, the following EEC was calculated:

Difenoconazole: 12.08 ppb

iii. Input Data and Assumptions for Models

Surface Water

GENEEC is a single event model (one runoff event), but can account for spray drift from multiple applications. GENEEC is hardwired to represent a 10 ha field immediately adjacent to a 1 ha pond, 2 m deep with no outlet. The pond receives a spray drift event from each application plus one runoff event, which moves a maximum of 10% of the applied pesticide into the pond. This runoff can be reduced by degradative processes in the field and by the effects of binding to soil in the field. In the GENEEC model, spray drift is equal to 1% of the applied for ground spray application and 5% for aerial application.

GENEEC does have certain limitations and is not an ideal tool for use in drinking water risk assessments. Surface-water-source drinking water tends to come from bodies of water that are substantially larger than a 1 hectare pond. Furthermore, GENEEC assumes that essentially the whole basin receives an application of the chemical. In virtually all cases, basins large enough to support a drinking water facility will contain a substantial fraction of area which does not receive the chemical. Furthermore, the persistence of the chemical near the drinking water facility is usually overestimated because there is always at least some flow in a river or turn over in a reservoir or lake.

Although GENEEC does have these limitations, it can be used in screening calculations and does provide an upper bound on the concentration of pesticide that can be found in drinking water. If a risk assessment based on GENEEC does not exceed the level of concern, then the actual risk is not likely to be exceeded. However, since GENEEC can substantially overestimate true drinking water concentrations, it will be necessary to refine the GENEEC estimate when the level of concern is exceeded. In those situations where the level of concern is exceeded and the GENEEC value is a substantial part of the total exposure, EFED can use a variety of methods to refine the exposure estimates.

Due to insufficient data to complete a quantitative environmental fate and transport assessment, difenoconazole is assumed to be persistent (t ½ = 365 days) and highly mobile (K oc = 0.0). The maximum difenoconazole application rate is 0.01498 lbs ai /A, which accounts for a maximum wheat application rate of 60 lbs seed/A treated with 11 g ai/100 kg seed. These modeling assumptions are expected to yield highly conservative estimates of difenoconazole in drinking water. The estimated maximum concentration of difenoconazole in surface water following application to non-crop areas is **0.837 ppb** and the 56-day average concentration is **0.835 ppb**. GENEEC

estimates represent an upper bound on the maximum and average concentrations of difenoconazole in surface waters as a result of this use (Memo, J. Hetrick, 10/28/98).

Ground Water

SCI-GROW (Screening Concentration In Ground Water) is an empirical screening model based on actual ground water monitoring data collected from small-scale prospective ground water monitoring studies for the registration of a number of pesticides that serve as benchmarks for the model. The current version of SCI-GROW provides realistic estimates of pesticide concentrations in shallow, highly vulnerable ground water (i.e., sites with sandy soils and depth to ground water of 10 to 20 feet). There may be exceptional circumstances under which concentrations of a pesticide may exceed the SCI-GROW estimates; however, such exceptions should be rare since the SCI-GROW model is based exclusively on ground water concentrations resulting from studies conducted at sites (shallow ground water and coarse soils) and under conditions (high irrigation) most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average concentration recorded during the sampling period. Because of the conservative nature of the monitoring data on which the model is based, SCI-GROW provides an upper bound estimate of pesticide residues in water. Because of the belief that pesticide concentrations in ground water do not fluctuate widely, SCI-GROW provides one concentration estimate to be used as a maximum and an average pesticide concentration value in ground water.

Due to insufficient data to complete a quantitative environmental fate and transport assessment, difenoconazole is assumed to be persistent (t ½ = 365 days) and highly mobile (K oc = 0.0). The maximum difenoconazole application rate is 0.01498 lbs ai /A, which accounts for a maximum wheat application rate of 60 lbs seed/A treated with 11 g ai/100 kg seed. These modeling assumptions are expected to yield highly conservative estimates of difenoconazole in drinking water. The concentration estimated in ground water is **12.08 ppb** The estimate from SCI-GROW represents an upper bound on the concentration of difenoconazole in ground waters as a result of non-crop use (Memo, J. Hetrick, 10/28/98).

c. Dietary Risk Assessment and Characterization

i. Chronic Risk (TMRC)

A chronic dietary risk assessment is required for difenoconazole. The RfD used for the chronic dietary analysis for difenoconazole is **0.01** mg/kg bwt/day.

Chronic dietary exposure estimates for difenoconazole are summarized in Attachment 1 (analysis dated 10/19/98). A chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the TMRC for the general population and 28 subgroups. The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. The chronic DEEM™ used mean consumption and gave the results listed in Table 5:

Table 5. Chronic DEEM™ Results Using Mean Consumption Data- Difenoconazole

Subgroups	Exposure (mg/kg/day)	% RfD
U.S. Population (48 states)	0.000558	5.6
Non-Hispanic other than black or white	0.000602	6.0
All infants (< 1 year)	0.000741	7.4
Nursing Infants (< 1 year old)	0.000274	2.7
Non-Nursing Infants (< 1 year old)	0.000938	9.4
Children (1-6 years old)	0.001368	13.7
Children (7-12 years old)	0.000878	8.8
Females (13+/nursing)	0.000504	5.0
Males (13-19 years)	0.000603	6.0

HED does not consider the chronic dietary risk to exceed the level of concern.

ii. Carcinogenic Risk

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), the CPRC classified difenoconazole as a **possible human carcinogen** (Memo, Jess Rowland and Esther Rinde, 7/27/94). The Committee recommended that a non-linear approach (MOE) for human risk characterization and extrapolation of risk be conducted using the NOAEL from the 2 year mouse study. Using the NOAEL of 4.7 mg/kg/day determined by HIARC, the dietary cancer MOE was determined to be **8400** for the U.S. population. Since the calculated cancer MOE is well above 100, the cancer risk does not exceed HED's level of concern.

Cancer $_{dietary}$: = **8400**

$$Cancer\ MOE = \frac{NOAEL\ (4.7\ mg/kg/day)}{Exposure\ for\ U.S.\ Population\ (0.000558\ mg/kg/day)} = 8400$$

iii. Acute Dietary Risk

An acute dietary risk assessment is required for difenoconazole. The acute NOAEL of **25** mg/kg/day based on post-implantation loss and resorption/dose and a significant decrease in fetal weight at 75 mg/kg/day during days 7 and 19 of gestation. The acute RfD is **0.25** mg/kg/day. HED's detailed acute analysis estimated the distribution of single-day exposures for females (13+ years old). A dose and endpoint were not selected for the general U.S. population and infants and children because there were no effects observed in oral toxicological studies including maternal toxicity in the developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure) (Memo, A. Kocialski and Jess Rowland, 9/25/98). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 CSFII and accumulated exposure to the chemical for each commodity. Each analysis assumes uniform distribution of difenoconazole in the commodity supply.

The acute exposure analysis was performed using tolerance level residues and 100 percent crop treated (Attachment 1).

Total from new and published tolerances at the 95th percentile are listed in Table 6.

Table 6. Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
Females (13+/pregnant/not nursing)	0.000913	<1
Females (13+/nursing)	0.001079	<1
Females(13-19 yrs/not preg. or nursing)	0.000941	<1
Females (20+ years/not preg. or nursing)	0.000804	<1
Females (13-50 years)	0.000869	<1

HED does not consider the acute dietary risk to exceed the level of concern.

iv. Drinking Water Risk (Acute, Chronic and Cancer)

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit

on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

OPP has calculated DWLOCs for acute exposure to difenoconazole in drinking water for females (13+ years old, nursing) to be **7500 ppb**. For chronic (non-cancer), the DWLOCs are **330** and **97 ppb** for the U.S. population and nursing infants (less than 1 year old), respectively. For cancer, the DWLOC is **1600 ppb**. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™ analysis) was subtracted from the RfD to obtain the acceptable acute exposure to difenoconazole in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to difenoconazole in drinking water. To calculate the DWLOC for cancer exposure relative to a cancer toxicity endpoint, the dietary food exposure (from DEEM™) was subtracted from the maximum acceptable exposure to obtain the acceptable cancer exposure to difenoconazole in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures.

Calculations:

$$DWLOC\ (\mu g/L) = \frac{water\ exposure\ (mg/kg/day)\ x\ (body\ weight)}{consumption\ (L)\ x\ 10^{-3}\ mg/\mu g}$$

The 2 liters (L) of drinking water consumed per day by adults and the 1 L per day consumed by children are default assumptions. The Agency's default body weights are: males - 70kg, females - 60kg, and children - 10 kg. Tables 7, 8, and 9 summarize the exposure and chronic, acute, and cancer DWLOCs.

Table 7. Chronic Scenario

Subpopulation	Food Exposure (from DEEM™ in mg/kg/day)	Maximum Water Exposure[1] (mg/kg)	RfD mg/kg/day	SCI-GROW[2] (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.000558	0.00944	0.01	12.08	0.837	330
Females (13+ yrs/nursing)	0.000504	0.00950	0.01	12.08	0.837	7500
Children (1-6 years old)	0.00274	0.00973	0.01	12.08	0.837	97

[1] Maximum Water Exposure(mg/kg/day) = RfD (mg/kg/day) - TMRC from DEEM™ (mg/kg/day).
[2] The highest application rate was used.

U.S. Population: DWLOC = **330** ppb

$$DWLOC\ (ppb) = \frac{0.00944\ mg/kg/day\ x\ 70\ kg}{2\ L\ x\ 10^{-3}\ mg/\mu g} = 330\ ppb$$

Females (13+ yrs, nursing): DWLOC = **7500** ppb

$$DWLOC\ (ppb) = \frac{0.00950\ mg/kg/day\ x\ 60\ kg}{2\ L\ x\ 10^{-3}\ mg/\mu g} = 7500\ ppb$$

Nursing Infants(<1 yr): DWLOC = **97** ppb

$$DWLOC\ (ppb) = \frac{0.00973\ mg/kg/day\ x\ 10\ kg}{1\ L\ x\ 10^{-3}\ mg/\mu g} = 97\ ppb$$

Table 8. Acute Scenario

Subgroup	RfD (mg/kg /day)	NOAEL (mg/kg/day)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure (mg/kg)	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
Females (13+, nursing)	0.25	25	0.001079	0.249	12.08	0.837	7500

Table 9. Cancer Scenario

Subgroup	Acceptable MOE	NOAEL (mg/kg/day)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure (mg/kg)	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. population	100	4.7	0.000558	0.046442	12.08	0.837	1626

U.S. population: DWLOC = **1600** ppb

$$DWLOC\ (ppb) = \frac{0.046442\ mg/kg/day\ x\ 70\ kg}{2\ L\ x\ 10^{-3}\ mg/\mu g} = 1600\ ppb$$

The maximum estimated concentrations of difenoconazole in surface water are less than OPP's DWLOCs for difenoconazole in drinking water as a contribution to acute, chronic, and cancer aggregate exposure. Therefore, taking into account the uses proposed in this action, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to back-calculated "levels of comparison" for difenoconazole in drinking water. These DWLOCs in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of difenoconazole in surface waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate risk assessment process.

d. Statement of the adequacy of the dietary exposure database to assess infants' and children's exposure

The dietary (food and water) exposure database for difenoconazole is adequate to assess infants' and children's exposure.

7. Occupational/Residential Exposure and Risk Assessment/Characterization

a. Occupational and Residential Exposure

i. Summary of Use Patterns and Formulations

This occupational risk assessment addresses the use of Dividend™ (EPA reg. # 100-740), the **32.8% liquid** formulation of difenoconazole on wheat. Difenoconazole is a fungicide used as a systemic seed dressing to control certain seed-borne and soil-borne diseases. It is applied as a water-based slurry using standard slurry or mist-type commercial seed treaters. The product label specifies an application rate of 0.024 pounds active ingredient (a.i.) per one

hundred pounds of seed.

Difenoconazole is not currently registered for any residential uses. Therefore, no non-dietary, non-occupational exposure is anticipated.

ii. Seed Treatment Exposures and Assumptions

In a typical seed treatment facility, (according to Mr. Brad Russell of the Novartis Seed Treatment Facility (oral personal communication with Olga Odiott, 10/98)), treatment is usually done using automatic and computerized equipment. In the case of difenoconazole, due to the small amount usually used, the fungicide is added manually (via graduated cylinder) to the treatment tank. In addition, seed treater, baggers and sewers are also part of the operation. The work area is supplied with aspirators to minimize any potential inhalation exposure. For difenoconazole, this activity is usually performed 5 days a week for 2 to 3 weeks, 3 times per year. HED's exposure assessment is based on the assumptions in Table 10.

Table 10. Assumptions for Commercial Handler Exposure Assessments

Factors	Quantities/Units		Source
Worker involved in commercial seed treatment	mixer/operator, bagger, bag sewer		Study: Worker Exposure to Apron Flowable While Treating Seed Commercially
Bag size	50 lbs.		
Bags produced per hour	250		
Hours worked per day	8		
Personal Protective Equipment worn by Mixer	Chemical apron, goggles, gloves		
Personal Protective Equipment worn by Bagger and Bag Sewer	Long-sleeved-shirt, long pants		
Mixer unit exposures (mg/kg ai handled)	Dermal: 0.0610	Inhalation: 0.000775	
Bag sewer unit exposures (mg/kg ai handled)	Dermal: 0.0346	Inhalation: 0.0056	
Bagger unit exposures (mg/kg ai handled)	Dermal: 0.0182	Inhalation: 0.000518	
Application rate	0.024 lb ai/100 lbs seed		label

Factors	Quantities/Units	Source
Worker involved in commercial seed treatment	mixer/operator, bagger, bag sewer	
Bag size	50 lbs.	
Application Type	commercial mist-type seed treatment equipment	
Days worked per week	5	Mr. Brad Russell, Novartis Seed Treatment Facility
Weeks worked per year	9	Study: Worker Exposure to Apron Flowable While Treating Seed [illegible] exposure

HED has very limited data for seed treatment scenarios. Therefore, exposure estimates for commercial seed treaters are based on data from a study entitled **Worker exposure to Apron Flowable while treating seed commercially** (Ciba-Geigy, 1993) submitted in support of MAXIM 4FS. This study was reviewed by HED in August of 1994 (Memo, B. Kitchens, 9/23/94).

This study determined the amount of active ingredient that mixer/operators, baggers and bag sewers were exposed to during the commercial treatment of seed. Both the study and the wheat use are for a liquid flowable formulation and employ the use of a mist-type applicator. The study was considered supplemental but upgradable by HED, pending the registrant's response to questions concerning field recoveries and ambient conditions. However, the study is the best body of data available for commercial seed treatment operations. The reviewer notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Environ. Contam.Toxicol. 31, 244-250, Grey, Marthre and Rogers, 1983).

iii. Commercial Seed Treater Exposure Assessment

Lifetime Average Daily Dose (LADD) calculation for commercial seed treaters were done assuming 5 days worked per week for 3 weeks each year. This operation generally takes place 3 times per year (oral personal communication from Mr. Russell of Novartis Seed Treatment Facility to Olga Odiott, 10/98, written confirmation to follow). Further, the LADD calculation assumes that the individual would work 35 out of 75 years.

Based on use patterns, only short-term dermal exposures are expected. Although as inhalation endpoint (any time-period) was not selected for difenoconazole, for purposes of the cancer risk calculations, inhalation exposures were estimated and added to the dermal exposures.

Table 11 summarizes the HED/RAB1 estimates for exposure for commercial

seed treaters including mixer/loaders, baggers and bag sewers.

Table 11. Seed Treatment Exposure to Dividend™ fungicide*

Job Function	Dermal Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE
Mixer/Operator	0.0083	0.00014	3005	0.00052	9.0×10^3
Bag Sewers	0.0047	0.0010	5299	0.00035	1.3×10^4
Bagger	0.0025	0.000094	10070	0.00016	3.0×10^4

The following equations were used to determine the expected worker exposures resulting from the commercial seed treatment applications of difenoconazole on wheat.

$$\text{MOE}_{\text{short - term dermal}} = \frac{\text{NOAEL}(25\ \text{MG / KG / DAY})}{\text{ADD}}$$

$$\text{ADD} = \left(\left(\text{UNIT EXPOSURE}\left(\frac{\text{MG}}{\text{KG AI}}\right) \right) \times \left(\frac{1\text{KG}}{2.2\ \text{LBS}}\right) \times \left(\text{APPLICATION RATE}\left(\frac{\text{LBS AI}}{100\ \text{LBS SEED}}\right)\right) \times \left(\frac{\text{SEED}}{\text{BAG}}\right) \times \left(\frac{\text{BAGS}}{\text{HOUR}}\right) \times \left(\frac{\text{HOURS}}{\text{DAY}}\right) \times \left(\frac{1}{\text{BODY WIEGHT(KG)}}\right) \right) \times 0.75(\text{dermal absorption})$$

$$\text{LADD} = \text{ADD}_{\text{inhalation \& dermal}} \times \left(\frac{\text{Days Worked per Year}}{\text{Total Days per Years}}\right) \times \left(\frac{35\ \text{Years Worked}}{70\ \text{Year Lifetime}}\right)$$

$$\text{CANCER MOE} = \frac{\text{NOAEL}\ (4.7\ \text{MG / KG / DAY})}{\text{LADD}}$$

iv. Farm Worker Exposures and Assumptions

Since wheat is planted mechanically, the potential agricultural worker exposures to difenoconazole are expected to be minimal. Wheat planting usually consists of two functions; mixer/loader and driver/planter. The highest amount of exposure is expected for the mixer/loader scenario, opening the treated seed bags and emptying the contents into the application equipment. The driver/planter is not expected to receive significant exposure.

PHED data was used to estimate exposure to workers. Currently, PHED does not contain data on this specific scenario. Therefore, the closest possible match is GRANULAR OPEN MIXING. The 'no gloves' unit exposure was used as a conservative assumption. The quality of the dermal data is considered '**low confidence**' (ABC grade, low replicates, and poor grade quality of hand replicates). The quality of the inhalation data is considered '**high confidence**' (AB grade, high replicates) (PHED v 1.1 Surrogate

Table).

Typical wheat planting-practice information, such as the number of acres that are planted per day and the pounds of seed planted per acre were obtained from the Texas Department of Agriculture (oral personal communication from Mr. Trostle to Olga Odiott, 10/98). The information considered in calculating exposures estimates is listed in Table 12.

Table 12: Mixer/Loader Exposure Assumptions

Scenario	Exposure	Unit Exposure (mg/lb ai)	Application Rate	Pounds seed /Acre	Acres /day[1]	Body Weight (kg)
Mixer/ Loader	Dermal	0.0084	0.024 lbs ai/100 lbs seed	75	500	60
Mixer/ Loader	Inhalation	0.0017	0.024 lbs ai/100 lbs seed	75	500	60
Source	- -	PHED 1.1 Surrogate Table. Granular open pour, no gloves	Label	TX Dept. of Agriculture	TX Dept. of Agriculture	Default value

[1] This information was based on the average amount of acres planted with wheat divided by the number of farms growing wheat. The relevant data have been taken from the 1992 Census of Agriculture.

v. Farm Worker Exposure Assessment

In calculating LADD, it was assumed that the farm worker would plant approximately 500 acres per day, 3 days per week for 2 weeks each year, for 35 years over a 70-year lifespan. Table 13 lists Mixer/Loader exposure estimates.

Exposure estimates where only done for the mixer/loader scenario, representing the highest possible exposure for all workers performing planting of treated seeds.

Table 13. Mixer/Loader Exposure to Dividend™ Treated Seeds

Job Function	Dermal Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE
Mixer/Loader	0.00095	0.00026	2.6×10^4	0.0000099	4.8×10^5

The following equations were used to determine the expected worker exposures resulting from the

opening and loading bags of wheat seed treated with difenoconazole.

$$MOE_{\text{short - term dermal}} = \frac{NOAEL(25\ MG\ /\ KG\ /\ DAY)}{ADD}$$

$$\text{MIXER / LOADER: } ADD = \left\{ \left(\left(\text{UNIT EXPOSURE} \left(\frac{MG}{LB\ AI} \right) \right) \times \left(\text{APPLICATION RATE} \left(\frac{LBS\ AI}{100\ LBS\ SEED} \right) \right) \right) \times \left(\frac{LBS\ SEED}{ACRE} \right) \times \left(\frac{ACRES}{DAY} \right) \times \left(\frac{1}{BODY\ WIEGHT\ (kg)} \right) \right\} \times 0.75 \text{ (dermal absorption)}$$

$$LADD = ADD_{\text{inhalation \& dermal}} \times \left(\frac{\text{Days Worked per Year}}{\text{Total Days per Year}} \right) \times \left(\frac{\text{35 Years Worked}}{\text{70 Year Lifetime}} \right)$$

$$\text{CANCER MOE} = \frac{NOAEL\ (4.7\ MG\ /\ KG\ /\ DAY)}{LADD}$$

vi. Post-Application Exposures and Assumptions

a) Occupational

No post-application exposure will be due to the commercial seed treatment use of difenoconazole.

b) Residential

There are currently no residential uses for difenoconazole.

b. Occupation and Residential Risk Assessment/Characterization

i. Risks from Dermal, and Inhalation Exposures for Seed Treaters

Although there are uncertainties about the quality of the data, HED concludes that the potential risk will not exceed the levels of concern. HED's level of concern for difenoconazole are for MOEs below 100. Estimated MOE's are well above 100. The exposure assessment is based on the best body of data that is available to HED at this time. The reviewer notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Envirn. Contam.Toxicol. 31, 244-250, Grey, Marthre and Rogers, 1983).

ii. Risks from Dermal, and Inhalation Exposures for Farm Workers

HED's level of concern for difenoconazole are for MOEs below 100. Estimated MOE's are well above 100. Because planting of wheat is done mechanically, the mixer/ loader scenario indicates the highest exposure

activities for farm workers. Therefore, exposure estimates where only done for this group of farm workers.

iii. Risk from Residential Exposure

There are no residential uses for difenoconazole at this time.

iv. Risk from Post-Application Exposure

There are no post-application exposures related to this use of difenoconazole. It is strictly a commercial seed treatment product.

v. Restricted Entry Interval (REI)

Since difenoconazole is a commercial seed treatment product with no uses at or immediately before planting, no re-entry interval is established.

vi. Incident Reports

Incident report data is available for difenoconazole. Two cases have been reported in OPP's Incident Data System by the registrant. They consist of instances of human exposure (in Ohio and Minnesota) which both took place in 1995. Neither case was confirmed and it is not known whether the alleged cases sought medical attention for their symptoms. One case (that was not wearing protective clothing) complained of pain and tingling in the arms and blurred vision. The second case complained primarily of flu-like symptoms and redness of the hands. There were no reports of exposure or illness due to difenoconazole from 1993 to 1996 among 431,684 unintentional cases reported to the nation's poison control centers participating in the Toxic Exposure Surveillance System. The California Pesticide Illness Surveillance Program had no reports of difenoconazole-related illness from 1982 through 1995. Based on lack of incidents from these three sources, no changes in labeling are recommended.

c. Statement of the adequacy of the residential exposure data base to assess infants' and children's exposures

No risk assessment was performed because there are no residential uses for this product.

8. Aggregate Exposure and Risk Assessment/Characterization

There are no proposed or existing residential uses for difenoconazole and occupational uses of difenoconazole will not result in post-application residential exposure.

Therefore, aggregate exposure risk assessment will be limited to food and water only. Details concerning the assumptions used in deriving exposure estimates and risk characterizations were discussed previously in this document.

a. Acute Aggregate Exposure and Risk

From the acute dietary (food only) risk assessment, a high-end exposure estimate was calculated for the subgroup, females 13+ years old. For females 13+ years old, less than 1% of the RfD is occupied by dietary exposure (food only). The acute dietary exposure for females 13+ years old is below HED's level of concern.

An acute RfD is not established for the general population including infants and children because there were no effects observed in oral toxicity studies including maternal toxicity in the developmental toxicity studies in rats and rabbits attributable to a single exposure (Memo, A. Kocialski and Jess Rowland, 9/25/98).

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs for difenoconazole as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate acute risk assessment process.

b. Short- and Intermediate-Term Aggregate Exposure and Risk

Since no registered residential uses or exposure scenarios were identified for short- and intermediate-term exposure scenarios, short- and intermediate-term aggregate risk assessments are not required (Memo, A. Kocialski and Jess Rowland, 9/25/98).

c. Chronic Aggregate Exposure and Risk

Chronic risk estimates associated with exposure to difenoconazole in food and water do not exceed HED's level of concern. The DEEM™ chronic exposure analysis used tolerance level residues and 100 percent crop treated information to estimate the TMRC for the general population and 28 subgroups. HED has

concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of difenoconazole is less than 14% for all populations. The estimated average concentrations of difenoconazole in surface and ground water are less than HED's DWLOCs for difenoconazole as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty, that residues of difenoconazole in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time considering the present uses and uses proposed in this action.

HED bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate chronic risk assessment process.

d. Cancer Aggregate Exposure and Risk

HED's level of concern for cancer is for MOEs that are greater than 100. Cancer risk estimate associated with exposure to difenoconazole for dietary exposure does not exceed HED's level of concern.

In accordance with the Agency's Proposed Guidelines for Carcinogenic Risk Assessment (April 26, 1996), the HED Cancer Assessment Review Committee classified difenoconazole as a **possible human carcinogen.** The Committee recommended that a non-linear MOE approach (Memo, Jess Rowland and Esther Rinde, 7/27/94).

From the cancer dietary risk assessment, a dietary exposure estimate of was calculated for the U.S. population. Table 14 shows the dietary exposure and cancer MOE of the U.S. population.

Table 14. Dietary Cancer Risk

Subgroup	Dietary Exposures (mg/kg/day)	Cancer MOE
U.S. population	0.000558	8400

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs for difenoconazole as a contribution to cancer aggregate exposure. Therefore, OPP concludes with reasonable certainty that

residues of difenoconazole in drinking water do not contribute significantly to the aggregate cancer human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate cancer risk assessment process.

9. Other Food Quality Protection Act (FQPA) Considerations

a. Cumulative Risk

Difenoconazole is a member of the **triazole** class of pesticides. Other members of this class include cyproconazole, fenbuconazole, propiconazole, tebuconazole, and uniconazole.

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. There are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this

tolerance action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether difenoconazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenoconazole need to be modified or revoked.

b. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety

US Population, Infants, and Children

Using the exposure assumptions described in this document, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of difenoconazole is less than 14% of the RfD for all populations. For the acute dietary of the high-risk subpopulation, the % RfD of difenoconazole are not expected to exceed 1% in females (13+). HED has concluded that the lifetime risk that will be utilized by cancer dietary (food only) MOE to residues of difenoconazole was 8400 for the U.S. population. Despite the potential for exposure to difenoconazole in drinking water, HED does not expect the acute, chronic, or cancer risk to exceed HED's level of concern. HED concludes that there is a reasonable certainty that no harm will result to infants and children from acute, chronic or cancer aggregate exposure to difenoconazole residues.

III. ACTIONS REQUIRED BY PETITIONER

A. Additional Generic Data Requirements

1. **Toxicological Studies** - None

2. **Chemistry** - None

3. **Occupational and Residential Exposure** - None

IV. REFERENCES

DP Barcode(s): D205118
Subject: PP# 2F04107. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 6/30/94.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 7/20/94
MRID(s): 432924-01

DP Barcode(s): D203644 and D203645
Subject: PP# 2F04107. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 5/18/94.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 6/16/94
MRID(s): 432365-01 thru -03

DP Barcode(s): D194842, D199810, D199580, and D195868
Subject: PP# 2F04107. Difenoconazole (Dividend) in/on Wheat, Barley, and Animal RACs. Review of Residue Data and Analytical Methodology.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM and Albin Kocialski, Head
Dated: 3/30/94
MRID(s): 428180-01 thru -06; 422451-41; 422451-01; 431203-01

DP Barcode(s): D172067 and D178394
Subject: PP# 2E4051. CGA-169374 (Difenoconazole, Dividend) in Imported Wheat, Barley, and Rye Grain. First Food Use.
From: Robert Lascola, Chemist
To: James Stone/Cynthia Giles-Parker
Dated: 10/26/92
MRID(s): 420900-01 thru -04; 420900-32; 420900-59; 423039-01

DP Barcode(s): D194842, D199810, D199580, and D195868
Subject: PP# 2F04107. Difenoconazole (Dividend) in/on Wheat and Barley. Results of Petition Method Validation for Animal Commodities.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 6/2/94
MRID(s): 428180-04 thru -05

DP Barcode(s): D210080

Subject: ID# 000100-00740. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 11/21/94.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 1/18/95
MRID(s): 434679-01 thru -03

DP Barcode(s): D217119, D217120, and D217121
Subject: ID# 000100-00740. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 6/29/95.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 9/13/95
MRID(s): 437037-01 thru -02

DP Barcode(s): None
Subject: PP# 2F04107 and PP#2E4051. Difenoconazole (Dividend). Issues to be presented to the HED Metabolism Committee on 7/14/94
From: G.F. Kramer, Ph.D., Chemist
To: HED Metabolism Committee
Dated: 7/12/94
MRID(s): None

DP Barcode(s): None
Subject: Metabolism Committee Meeting of 7/14/94. PP# 2F4107 and PP# 2E4051. Difenoconazole (Dividend).
From: G.F. Kramer, Ph.D., Chemist
To: HED Metabolism Committee
Dated: 7/22/94
MRID(s): None

DP Barcode(s): D216521
Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Evaluation of Residue Data and Analytical Methods.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 2/23/96
MRID(s): 436732-01 thru -14

DP Barcode(s): D229926
Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Amendment of 8/20/96. Revised Sections B and F and Submission of Confirmatory Method.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 10/4/96
MRID(s): 440933-01 thru -02

DP Barcode(s): D230853
Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Amendment of 9/30/96. Revised Section F.
From: G.F. Kramer, Ph.D., Chemist
To: Debbie McCall, Acting Section Head
Dated: 11/13/96
MRID(s): 440933-01 thru -02

DP Barcode(s): D249863
Subject: PP#5E4526. Difenoconazole in or on Imported Bananas. Amendments of 2/21/97 and 3/19/98.
From: Susie Chun, Chemist
To: Cynthia Giles-Parker, PM
Dated: 11/2/98
MRID(s): 445189-00 thru -04.

DP Barcode(s): D248285 and D248419
Subject: PP#2F4107. Difenoconazole (Dividend®) in/on Wheat and Animal RACs. Amendments of 7/8/98 and 7/30/98.
From: Susie Chun, Chemist
To: Cynthia Giles-Parker, PM
Dated: 10/28/98
MRID(s): 446020-00 thru -01; 446194-01.

DP Barcode(s): None
Subject: Difenoconazole - Report of the FQPA Safety Factor Committee.
From: Brenda Tarplee, Executive Secretary
To: Melba Morrow, Branch Senior Scientist
Dated: 10/28/98
MRID(s): None

DP Barcode(s): None
Subject: Difenoconazole - Report of the Hazard Identification Assessment Review Committee.
From: Albin Kocialski, Toxicologist and Jess Rowland, Executive Secretary
To: George Kramer, PhD, Chemist
Dated: 9/25/98
MRID(s): None

DP Barcode(s): None
Subject: Tier 1 FQPA Drinking Water Assessment for Difenoconazole
From: James Hetrick, PhD, Senior Physical Scientist
To: Cynthia Giles-Parker, PM
Dated: 10/28/98
MRID(s): None

DP Barcode(s): D250090, D250397 and D250398
Subject: Dietary Exposure Analysis for Difenoconazole in/on Wheat and Animal Commodities (2F4107), Import Bananas (5E4526), and Sweet Corn (98ID0040). Chemical#: 128847.
From: Susie Chun, Chemist
To: Dana Vogel, Chemist
Dated: 10/20/98
MRID(s): None

DP Barcode(s): None
Subject: Carcinogenicity Peer Review of Difenoconazole [Dividend]
From: Jess Rowland, Toxicologist and Esther Rinde, Ph.D
To: Cynthia Giles-Parker, PM
Dated: 7/27/94
MRID(s): None

DP Barcode(s): D189836
Subject: Difenoconazole: Registrant's Response to Deficiencies Cited in Toxicology Review.
From: Jess Rowland, M.S., Acting Section Head
To: Cynthia Giles-Parker, PM
Dated: 9/15/93
MRID(s): 42710010, 42710008, 42710006, 4271005, 42090014 thru 20

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Rats
From: Ciba-Geigy Corporation
To:
Dated: 1987
MRID(s): 429090022

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Difenoconazole: 28-week Feeding Study in Dogs
From: Ciba-Geigy Corporation
To:
Dated: 1987
MRID(s): 429090012

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Mice
From: Ciba-Geigy Corporation
To:

Dated: 1987
MRID(s): 429090021

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Rats
From: Ciba-Geigy Corporation
To:
Dated: 1987
MRID(s): 429090022

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Difenoconazole: 21-day Dermal Study in Rabbits
From: Ciba-Geigy Corporation
To:
Dated: 1987
MRID(s): 429090013

Study: Potential Exposure of Commercial Seed-treating Applicators to the Pesticides Carboxim-Thiram and Lindane.
Authors: W.E. Grey, D.E. Marthre, S.J. Rogers
Location: Bulletin of Environmental Contamination and Toxicology 31, 244-250.
Dated: 1983

ATTACHMENTS

I. Dietary exposure analyses for difenoconazole, 10/20/98
II. Drinking Water Assessment for difenoconazole, 10/28/98
III. Metabolism Committee Flow Chart: Carcinogenicity Peer Review of Difenoconazole, 5/18/94

cc: PP#5E04526,PP#2F4107, S. Chun, A. Kocialski, D. Vogel)
RDI: Team (11/18/98), RAB1 Chemists (11/19/98); M. Morrow (11/17/98); Risk SARC (12/1/98)
D. Vogel: 804F:CM#2:(703)305-0874

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: October 20, 1998

SUBJECT: Dietary Exposure Analysis for Difenoconazole in/on Wheat and Animal Commodities (2F4107), Import Bananas (5E4526), and Sweet Corn (98ID0040). Chemical#: 128847. DP Barcodes: D250090, D250397, and D250398.

FROM: Susie Chun, Chemist
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Melba Morrow, D.V.M., Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

TO: Dana Vogel, Chemist
Registration Action Branch 1
Health Effects Division (7509C)

Action Requested

Provide an estimate of the dietary exposure and associated risk for difenoconazole resulting from existing tolerances and proposed tolerance levels for import bananas (5E4526) and sweet corn (98ID0040).

The proposed tolerance levels of 0.2 ppm in/on bananas as a result of a Section 3 request (5E4526) and 0.1 ppm in/on sweet corn as a result of a Section 18 request (98ID0040) were used in this analysis. *Note: Existing time-limited tolerances for the wheat and animal commodities expire 12/31/98.*

Toxicological Endpoints

Acute

The acute analysis for difenoconazole used an acute NOAEL = 25 mg/kg/day based on post-implantation loss and resorption/doe and a significant decrease in fetal weight at 75 mg/kg/day (LOAEL) resulting in an acute reference dose (aRfD) of 0.25 mg/kg/day. The acute dietary risk assessment is required for the protection of the **Females 13+** subgroup population from acute exposure to difenoconazole. For the general population (including infants and children), a dose

and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose] (Memo, A. Kocialski and J. Rowland, 9/25/98).

Chronic

For the chronic analysis, the HIARC selected a NOAEL=0.96 mg/kg/day based on cumulative decreases in body weight gains at 500 ppm [24.12 mg/kg/day (LOAEL)]. This resulted in a chronic RfD of 0.01 mg/kg/day (Memo, A. Kocialski and J. Rowland, 9/25/98).

FQPA Recommendation

The HIARC, based on hazard assessment, recommends to the FQPA Safety Committee, that 10x factor for the protection of infants and children should be removed because:

A) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits;

B) The two generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults; and

C) There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies. Neither brain weight nor histopathology (perfused or nonperfused) of the nervous system was affected in the subchronic and chronic toxicity studies.

D) The toxicology data base is complete and there are no data gaps.

This decision was confirmed by the FQPA Safety Factor Committee, which met on October 19, 1998.

Residue Information

Tolerances for difenoconazole (including time-limited tolerances) are published in 40 CFR §180.475. For the acute and chronic analysis, published, proposed new tolerance level residues, and 100% crop treated (%CT) were used.

Results

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. A summary of the residue information used in the acute and chronic analyses is attached (Attachment 1).

Acute Exposure Analysis

The acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of cymoxanil in the commodity supply.

Since the HIARC determined that the only subgroup population of interest was females (13+), no acute dietary analysis was performed for the U.S. General Population or Infants and Children. The acute exposure analysis for female (13+) subgroup was performed using tolerance level residues and 100 percent crop treated (Attachment 2).

Total from new and published tolerances at the 95th percentile are shown in Table 1.

Table 1. - Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
Females (13+/pregnant/not nursing)	0.000913	< 1
Females (13+/nursing)	0.001079	< 1
Females(13-19 yrs/not preg. or nursing)	0.000941	< 1
Females (20+ years/not preg. or nursing)	0.000804	< 1
Females (13-50 years)	0.000869	< 1

Chronic Analysis

The chronic DEEM™ used mean consumption (3 day average). The results are in Table 2.

Table 2. - Chronic Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
U.S. Population (48 states)	0.000558	5.6
Non-hispanic other than black or white[3]	0.000602	6.0
All infants (< 1 year)	0.000741	7.4
Nursing Infants (< 1 year old)	0.000274	2.7
Non-Nursing Infants (< 1 year old)	0.000938	9.4
Children (1-6 years old)	0.001368	13.7
Children (7-12 years old)	0.000878	8.8
Females (13+/nursing)	0.000504	5.0
Males (13-19 years)	0.000603	6.0

The complete chronic analysis is attached (Attachment 3).

Conclusions

The acute analysis for difenoconazole is a very conservative estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated. All %RfDs from this analysis were below 1% for the subgroup, females 13+. The results of this analysis indicate that the acute dietary risk associated with the proposed uses of difenoconazole in/on wheat and animal commodities is below the Agency's level of concern.

The results of the chronic analysis indicate that the chronic dietary risk associated with the proposed uses of difenoconazole is below the Agency's level of concern.

Attachment 1: Residue File
Attachment 2: Acute DEEM™ analysis (S. Chun, 10/19/98)
Attachment 3: Chronic DEEM™ analysis (S. Chun, 10/19/98)

cc: S. Chun (RAB1); B. Steinwand (CEB1), 2F4107, 5E4526, 98ID0040
RDI: DRES Team (10/15/98)
S. Chun:804-F:CM#2:(703)305-2249:7509C:RAB1

Attachment 1 - Residue File

FILENAME: C:\deem89\resdata\128847.r91
FILENAME: C:\deem89\resdata\128847.r91
CHEMICAL NAME: Difenoconazole
RfD(CHRONIC): .010000 mg/kg/DAY NOEL(CHRONIC): .000000 mg/kg/day
RfD(ACUTE): .250000 mg/kg/DAY NOEL(ACUTE): 25.000000 mg/kg/day Q*=.0000
Date created/last modified: 10-05-1998/14:50:27/8 Program ver. 6.16
Comment: D. Vogel, 98ID0040 (corn), 2F4107 (wheat & animal), 5E4526 (bananas)

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
073	A	BANANAS-DRIED	000.200000		03.900	01.000	5E4526, New
378	A	BANANAS-JUICE	000.200000		01.000	01.000	5E4526, New
072	A	BANANAS	000.200000		01.000	01.000	5E4526, New
094	A	PLANTAINS-RIPE	000.200000		01.000	01.000	5E4526, New
481	A	PLANTAINS-DRIED	000.200000		03.900	01.000	5E4526, New
480	A	PLANTAINS-GREEN	000.200000		01.000	01.000	5E4526, New
265	O	BARLEY	000.100000		01.000	01.000	2E4051
237	O	CORN/POP	000.100000		01.000	01.000	S18, 98ID0040, New
267	O	CORN GRAIN-BRAN	000.100000		01.000	01.000	S18, 98ID0040, New
268	O	CORN GRAIN/SUGAR/HFCS	000.100000		01.500	01.000	S18, 98ID0040, New
266	O	CORN GRAIN-ENDOSPERM	000.100000		01.000	01.000	S18, 98ID0040, New
238	O	CORN/SWEET	000.100000		01.000	01.000	S18, 98ID0040, New
388	O	CORN GRAIN/SUGAR-MOLASSES	000.100000		01.500	01.000	S18, 98ID0040, New
289	O	CORN GRAIN-OIL	000.100000		01.000	01.000	S18, 98ID0040, New
273	O	RYE-GERM	000.100000		01.000	01.000	2E4051
272	O	RYE-ROUGH	000.100000		01.000	01.000	2E4051
274	O	RYE-FLOUR	000.100000		01.000	01.000	2E4051
277	O	WHEAT-GERM	000.100000		01.000	01.000	2F4107, TLT 12/31/98
278	O	WHEAT-BRAN	000.100000		01.000	01.000	2F4107, TLT 12/31/98
279	O	WHEAT-FLOUR	000.100000		01.000	01.000	2F4107, TLT 12/31/98
437	O	WHEAT-GERM OIL	000.100000		01.000	01.000	2F4107, TLT 12/31/98
276	O	WHEAT-ROUGH	000.100000		01.000	01.000	2F4107, TLT 12/31/98
324	U	BEEF-FAT W/O BONES	000.050000		01.000	01.000	2F4107, TLT 12/31/98
325	U	BEEF-KIDNEY	000.050000		01.000	01.000	2F4107, TLT 12/31/98
326	U	BEEF-LIVER	000.050000		01.000	01.000	2F4107, TLT 12/31/98
327	U	BEEF-LEAN(FAT/FREE)W/O BONES	000.050000		01.000	01.000	2F4107, TLT 12/31/98
322	U	BEEF-OTHER ORGAN MEATS	000.050000		01.000	01.000	2F4107, TLT 12/31/98
323	U	BEEF-DRIED	000.050000		01.920	01.000	2F4107, TLT 12/31/98
321	U	BEEF-MEAT BYPRODUCTS	000.050000		01.000	01.000	2F4107, TLT 12/31/98
332	U	GOAT-LIVER	000.050000		01.000	01.000	2F4107, TLT 12/31/98
329	U	GOAT-OTHER ORGAN MEATS	000.050000		01.000	01.000	2F4107, TLT 12/31/98
333	U	GOAT-LEAN (FAT/FREE) W/O BONE	000.050000		01.000	01.000	2F4107, TLT 12/31/98
331	U	GOAT-KIDNEY	000.050000		01.000	01.000	2F4107, TLT 12/31/98
328	U	GOAT-MEAT BYPRODUCTS	000.050000		01.000	01.000	2F4107, TLT 12/31/98
330	U	GOAT-FAT W/O BONE	000.050000		01.000	01.000	2F4107, TLT 12/31/98

334	U	HORSEMEAT	000.050000	01.000 01.000	2F4107, TLT 12/31/98
347	U	PORK-LEAN (FAT FREE) W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
346	U	PORK-LIVER	000.050000	01.000 01.000	2F4107, TLT 12/31/98
345	U	PORK-KIDNEY	000.050000	01.000 01.000	2F4107, TLT 12/31/98
344	U	PORK-FAT W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
343	U	PORK- OTHER ORGAN MEATS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
342	U	PORK-MEAT BYPRODUCTS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
335	U	RABBIT	000.050000	01.000 01.000	2F4107, TLT 12/31/98
338	U	SHEEP-FAT W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
337	U	SHEEP-OTHER ORGAN MEATS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
336	U	SHEEP-MEAT BYPRODUCTS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
339	U	SHEEP-KIDNEY	000.050000	01.000 01.000	2F4107, TLT 12/31/98
340	U	SHEEP-LIVER	000.050000	01.000 01.000	2F4107, TLT 12/31/98
341	U	SHEEP-LEAN (FAT FREE)W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
424	U	VEAL-FAT W/O BONES	000.050000	01.000 01.000	2F4107, TLT 12/31/98
425	U	VEAL-LEAN (FATFREE) W/O BONES	000.050000	01.000 01.000	2F4107, TLT 12/31/98
430	U	VEAL-MEAT BYPRODUCTS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
426	U	VEAL-KIDNEY	000.050000	01.000 01.000	2F4107, TLT 12/31/98
427	U	VEAL-LIVER	000.050000	01.000 01.000	2F4107, TLT 12/31/98
428	U	VEAL-OTHER ORGAN MEATS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
429	U	VEAL-DRIED	000.050000	01.920 01.000	2F4107, TLT 12/31/98
368	V	CHICKEN-FAT W/O BONES	000.050000	01.000 01.000	2F4107, TLT 12/31/98
369	V	CHICKEN-LEAN/FATFREE W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
367	V	CHICKEN-GIBLETS(LIVER)	000.050000	01.000 01.000	2F4107, TLT 12/31/98
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	000.050000	01.000 01.000	2F4107, TLT 12/31/98
366	V	CHICKEN-BYPRODUCTS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
362	V	POULTRY-OTHER-FAT W/O BONES	000.050000	01.000 01.000	2F4107, TLT 12/31/98
360	V	POULTRY-OTHER-LEAN (FAT FREE)	000.050000	01.000 01.000	2F4107, TLT 12/31/98
361	V	POULTRY-OTHER-GIBLETS(LIVER)	000.050000	01.000 01.000	2F4107, TLT 12/31/98
357	V	TURKEY--FAT W/O BONES	000.050000	01.000 01.000	2F4107, TLT 12/31/98
356	V	TURKEY-GIBLETS (LIVER)	000.050000	01.000 01.000	2F4107, TLT 12/31/98
355	V	TURKEY-BYPRODUCTS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
449	V	TURKEY-OTHER ORGAN MEATS	000.050000	01.000 01.000	2F4107, TLT 12/31/98
358	V	TURKEY-LEAN/FAT FREE W/O BONE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
365	X	EGGS-YOLK ONLY	000.050000	01.000 01.000	2F4107, TLT 12/31/98
363	X	EGGS-WHOLE	000.050000	01.000 01.000	2F4107, TLT 12/31/98
364	X	EGGS-WHITE ONLY	000.050000	01.000 01.000	2F4107, TLT 12/31/98
319	X	MILK-FAT SOLIDS	000.010000	01.000 01.000	2F4107, TLT 12/31/98
398	X	MILK-BASED WATER	000.010000	01.000 01.000	2F4107, TLT 12/31/98
320	X	MILK SUGAR (LACTOSE)	000.010000	01.000 01.000	2F4107, TLT 12/31/98
318	X	MILK-NONFAT SOLIDS	000.010000	01.000 01.000	2F4107, TLT 12/31/98

Attachment 2: Acute Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:23 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day
Run Comment: D. Vogel, 98ID0040 (corn), 2F4107 (wheat & animal), 5E4526 (banan as)

Females (13+/preg/not nsg)

Daily Exposure Analysis 1/ (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000448	0.000448
Standard Deviation	0.000222	0.000222
Standard Error	0.000011	0.000011
Percent of aRfD	0.18	0.18

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000213	0.09	10.00	0.000768	0.31
80.00	0.000276	0.11	5.00	0.000913	0.37
70.00	0.000313	0.13	2.50	0.000976	0.39
60.00	0.000350	0.14	1.00	0.001182	0.47
50.00	0.000394	0.16	0.50	0.001279	0.51
40.00	0.000459	0.18	0.25	0.001327	0.53
30.00	0.000528	0.21	0.10	0.001400	0.56
20.00	0.000600	0.24			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000213	0.09	10.00	0.000768	0.31
80.00	0.000276	0.11	5.00	0.000913	0.37
70.00	0.000313	0.13	2.50	0.000976	0.39
60.00	0.000350	0.14	1.00	0.001182	0.47
50.00	0.000394	0.16	0.50	0.001279	0.51
40.00	0.000459	0.18	0.25	0.001327	0.53
30.00	0.000528	0.21	0.10	0.001400	0.56
20.00	0.000600	0.24			

1/ Analysis based on all three-day participant records in CSFII 1989-92 survey.

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DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:23 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day

Females (13+/nursing)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000504	0.000504
Standard Deviation	0.000290	0.000290
Standard Error	0.000020	0.000020
Percent of aRfD	0.20	0.20

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000169	0.07	10.00	0.000947	0.38
80.00	0.000246	0.10	5.00	0.001079	0.43
70.00	0.000310	0.12	2.50	0.001178	0.47
60.00	0.000386	0.15	1.00	0.001303	0.52
50.00	0.000443	0.18	0.50	0.001389	0.56
40.00	0.000529	0.21	0.25	0.001432	0.57
30.00	0.000623	0.25	0.10	0.001458	0.58
20.00	0.000752	0.30			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000169	0.07	10.00	0.000947	0.38
80.00	0.000246	0.10	5.00	0.001079	0.43
70.00	0.000310	0.12	2.50	0.001178	0.47
60.00	0.000386	0.15	1.00	0.001303	0.52
50.00	0.000443	0.18	0.50	0.001389	0.56
40.00	0.000529	0.21	0.25	0.001432	0.57
30.00	0.000623	0.25	0.10	0.001458	0.58
20.00	0.000752	0.30			

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:23 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day

Females (13-19 yrs/np/nn)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000482	0.000483
Standard Deviation	0.000259	0.000258
Standard Error	0.000006	0.000006
Percent of aRfD	0.19	0.19

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000209	0.08	10.00	0.000833	0.33
80.00	0.000266	0.11	5.00	0.000941	0.38
70.00	0.000320	0.13	2.50	0.001071	0.43
60.00	0.000384	0.15	1.00	0.001240	0.50
50.00	0.000441	0.18	0.50	0.001582	0.63
40.00	0.000494	0.20	0.25	0.001762	0.70
30.00	0.000566	0.23	0.10	0.001862	0.74
20.00	0.000681	0.27			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000205	0.08	10.00	0.000833	0.33
80.00	0.000265	0.11	5.00	0.000941	0.38
70.00	0.000319	0.13	2.50	0.001071	0.43
60.00	0.000383	0.15	1.00	0.001240	0.50
50.00	0.000440	0.18	0.50	0.001581	0.63
40.00	0.000494	0.20	0.25	0.001762	0.70
30.00	0.000565	0.23	0.10	0.001862	0.74
20.00	0.000680	0.27			

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:23 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day

Females (20+ years/np/nn)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000376	0.000377
Standard Deviation	0.000226	0.000225
Standard Error	0.000002	0.000002
Percent of aRfD	0.15	0.15

Percent of Person-Days that are User-Days = 99.75%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000145	0.06	10.00	0.000676	0.27
80.00	0.000199	0.08	5.00	0.000804	0.32
70.00	0.000242	0.10	2.50	0.000943	0.38
60.00	0.000286	0.11	1.00	0.001129	0.45
50.00	0.000331	0.13	0.50	0.001318	0.53
40.00	0.000381	0.15	0.25	0.001497	0.60
30.00	0.000445	0.18	0.10	0.001682	0.67
20.00	0.000533	0.21			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000142	0.06	10.00	0.000676	0.27
80.00	0.000198	0.08	5.00	0.000804	0.32
70.00	0.000241	0.10	2.50	0.000942	0.38
60.00	0.000285	0.11	1.00	0.001129	0.45
50.00	0.000330	0.13	0.50	0.001318	0.53
40.00	0.000381	0.15	0.25	0.001496	0.60
30.00	0.000445	0.18	0.10	0.001682	0.67
20.00	0.000532	0.21			

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:24 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day

Females (13-50 years)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000403	0.000404
Standard Deviation	0.000238	0.000238
Standard Error	0.000002	0.000002
Percent of aRfD	0.16	0.16

Percent of Person-Days that are User-Days = 99.76%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000155	0.06	10.00	0.000721	0.29
80.00	0.000215	0.09	5.00	0.000869	0.35
70.00	0.000261	0.10	2.50	0.001010	0.40
60.00	0.000307	0.12	1.00	0.001188	0.48
50.00	0.000357	0.14	0.50	0.001412	0.56
40.00	0.000412	0.16	0.25	0.001562	0.62
30.00	0.000478	0.19	0.10	0.001715	0.69
20.00	0.000570	0.23			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000152	0.06	10.00	0.000721	0.29
80.00	0.000214	0.09	5.00	0.000869	0.35
70.00	0.000260	0.10	2.50	0.001010	0.40
60.00	0.000307	0.12	1.00	0.001188	0.48
50.00	0.000356	0.14	0.50	0.001412	0.56
40.00	0.000411	0.16	0.25	0.001561	0.62
30.00	0.000478	0.19	0.10	0.001715	0.69
20.00	0.000569	0.23			

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847.r91 Adjustment factor #2 NOT used.
Analysis Date: 10-19-1998/13:36:24 Residue file dated: 10-19-1998/13:33:14/8
Acute Reference Dose (aRfD) = 0.250000 mg/kg body-wt/day
Run Comment: D. Vogel, 98ID0040 (corn), 2F4107 (wheat & animal), 5E4526 (banan as)

Summary calculations:

	95th Percentile Exposure	95th Percentile % aRfD	99th Percentile Exposure	99th Percentile % aRfD	99.9 Percentile Exposure	99.9 Percentile % aRfD
Females (13+/preg/not nsg):	0.000913	0.37	0.001182	0.47	0.001400	0.56
Females (13+/nursing):	0.001079	0.43	0.001303	0.52	0.001458	0.58
Females (13-19 yrs/np/nn):	0.000941	0.38	0.001240	0.50	0.001862	0.74
Females (20+ years/np/nn):	0.000804	0.32	0.001129	0.45	0.001682	0.67
Females (13-50 years):	0.000869	0.35	0.001188	0.48	0.001715	0.69

Attachment 3: Chronic Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.12
DEEM89N CHRONIC analysis for DIFENOCONAZOLE (1989-92 data)
Residue file name: 128847 Adjustment factor #2 NOT used.
Analysis Date 10-19-1998 Residue file dated: 10-19-1998/13:33:14/8
Reference dose (RfD, CHRONIC) = 0.010000 mg/kg body-wt/day
COMMENT 1: D. Vogel, 98ID0040 (corn), 2F4107 (wheat & animal), 5E4526 (bananas)

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Pop - 48 states - all seasons	0.000558	5.6%
U.S. Population - spring season	0.000545	5.5%
U.S. Population - summer season	0.000563	5.6%
U.S. Population - autumn season	0.000566	5.7%
U.S. Population - winter season	0.000555	5.6%
Northeast region	0.000548	5.5%
Midwest region	0.000573	5.7%
Southern region	0.000562	5.6%
Western region	0.000541	5.4%
Pacific Region	0.000532	5.3%
Hispanics	0.000570	5.7%
Non-hispanic whites	0.000555	5.5%
Non-hispanic blacks	0.000559	5.6%
Non-hispanic other than black or white	0.000602	6.0%
All infants (<1 year)	0.000741	7.4%
Nursing infants (<1 year)	0.000274	2.7%
Non-nursing infants (<1 year)	0.000938	9.4%
Children (1-6 years)	0.001368	13.7%
Children (7-12 years)	0.000878	8.8%
Females (13-19 yrs/not preg. or nursing)	0.000483	4.8%
Females (20+ years/not preg. or nursing)	0.000380	3.8%
Females (13-50 years)	0.000404	4.0%
Females (13+/pregnant/not nursing)	0.000448	4.5%
Females (13+/nursing)	0.000504	5.0%
Males (13-19 years)	0.000603	6.0%
Males (20+ years)	0.000430	4.3%
Seniors (55+)	0.000383	3.8%

PC Code No: 128847

MEMORANDUM

SUBJECT Tier 1 FQPA Drinking Water Assessment for Difenoconazole

FROM: James Hetrick, Ph.D., Senior Physical Scientist
Environmental Risk Branch I
Environmental Fate and Effects Division

THRU: Arnet Jones, Branch Chief
Environmental Risk Branch I
Environmental Fate and Effects Division

TO: Cynthia Giles-Parker, PM 22
Registration Division (7505C)

The FQPA drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since difenoconazole is used solely as a fungicide on the seed coat of small grains (*e.g.*, wheat) to control soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. In order to conduct Tier 1 modeling for difenoconazole, the following assumptions were made: 1.) Complete dissociation of difenoconazole from the seed coat is assumed; 2.) Difenoconazole is persistent ($t_{1/2}$=365 days) and mobile (K_{oc}=0.0) in terrestrial and aquatic environments; and 3.) The maximum difenoconazole application rate is 0.01498 lbs ai /A, which accounts for a maximum wheat application rate of 60 lbs seed/A treated with 11 g ai/100 kg seed. The seeding rate for wheat was taken from information on the internet (http://www.cargill.com/aghorizons/sgronomics/planting.htm). These modeling assumptions are expected to yield highly conservative estimates of difenoconazole concentrations in drinking water. EFED recommends that the registrant submit aerobic soil metabolism and batch equilibrium data to provide a limited understanding on the fate and transport of difenoconazole. Additional environmental fate data (*e.g.*, terrestrial field dissipation) may be needed to confirm routes and rates of dissipation under actual use conditions.

Tier 1 GENEEC modeling for the maximum application rate of Dividend 0.31 FS (EPA Reg. No. 100-778) indicates the maximum (acute endpoint) and 56 day average (chronic endpoint) concentrations of difenoconazole in surface water are not likely to exceed 0.837 and 0.835 µg/L, respectively. The Tier 1 SCI-GROW modeling predicts that ground water concentrations of difenoconazole is not likely to exceed 12.08 µg/L.

Model Input Parameters

The following data were used for input into the Tier 1 GENEEC (version 1.2) and SCIGROW (version 1) modeling for difenoconazole:

Parameter	Value	Source
Soil K_{oc}	0 ml/g *	No Data
Aerobic soil half-life	365 days*	No Data
Aerobic aquatic half-life	Stable	No Data
Photolysis Half-life (pH 7)	Stable	No Data
Hydrolysis (pH 7)	Stable	MRID 42245127
Water Solubility	3,300 mg/l	Parsons 1/11/94

* Difenoconazole is assumed to be persistent ($t_{1/2}$=365 days) and highly mobile (K_{oc}=0.0) in the absence of data.

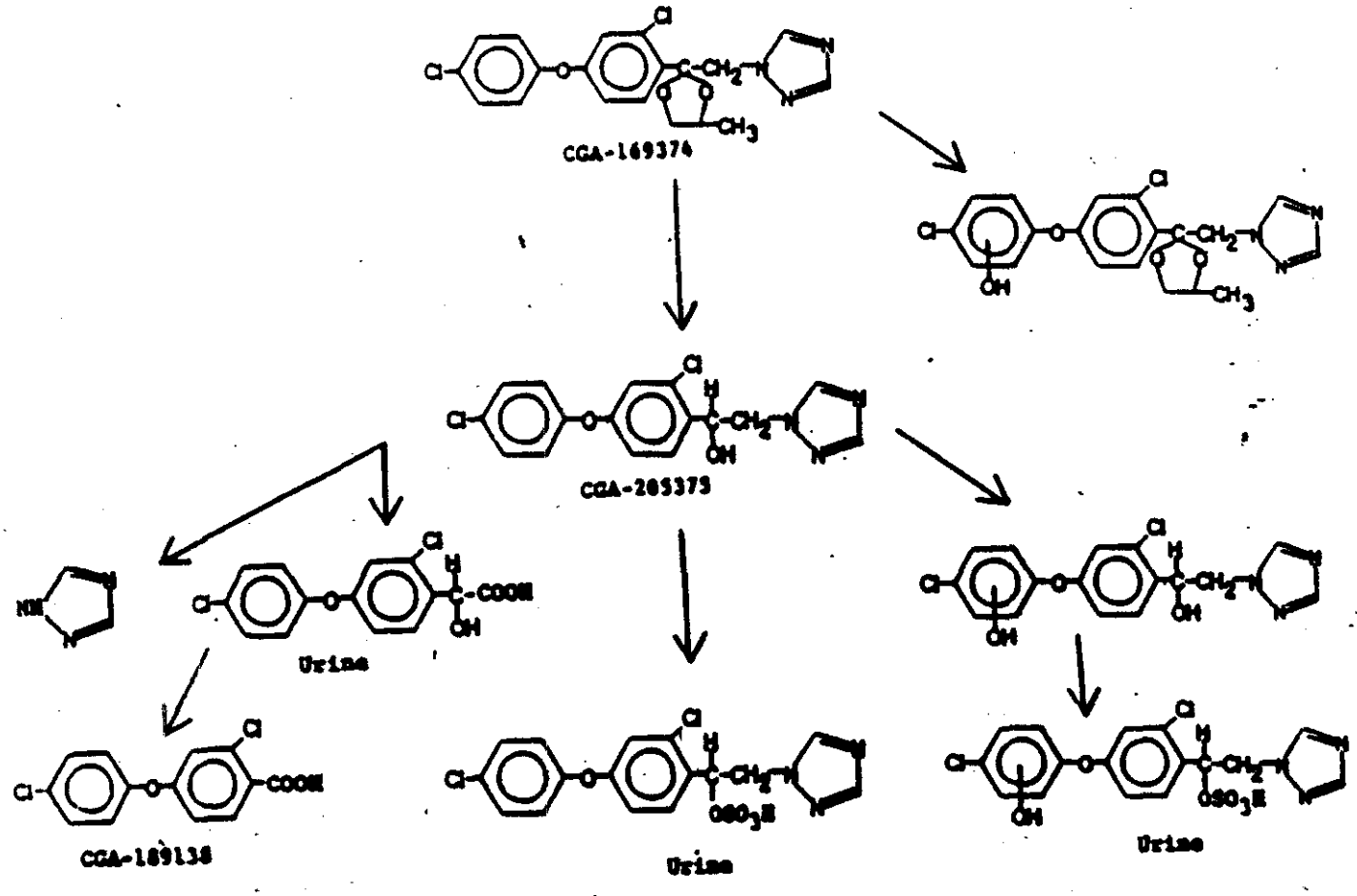


Figure 1. Proposed Metabolic Pathway of Difenoconazole [CGA 169374] in Rats.

SUPPLEMENTAL LABELING
Page 1 of 1

DIVIDEND® FUNGICIDE
EPA REG [redacted]

ACCEPTED
FEB 4 [illegible]
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 100-740

Active Ingredient:
[(2S,4R)/(2R,4S)]/[(2R,4R/2S,4S)]
1-{2-[4-(4-Chlorophenoxy)-2-chlorophenyl]-4-
methyl-1,3-dioxolan-2-yl-methyl}-1H-1,2,4-triazole ... [redacted]
Inert Ingredients: 67.2%
Total: 100.0%
100.0%

KEEP OUT OF REACH OF CHILDREN.

CAUTION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)

All applicable directions, restrictions, and precautions on the EPA-registered Dividend label are to be followed.

This label must be in the possession of the user at the time of planting or pesticide application.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

FAILURE TO FOLLOW THE DIRECTIONS FOR USE AND PRECAUTIONS ON THIS LABEL MAY RESULT IN POOR DISEASE CONTROL, CROP INJURY AND/OR ILLEGAL RESIDUES.

Do not plant any crop other than wheat within 30 days to fields which treated seeds were planted.

Dividend® trademark of Ciba-Geigy Corporation
U.S. Patent No. 5,266,585

Ciba Crop Protection
Seed Treatment Products
Ciba-Geigy Corporation
Greensboro, NC

CGA

Highlighted Version

Booklet Master Label

with COMMENTS
In EPA Letter Dated:

Jacket

AGU -

Under the Federal Insecticide Fungicide, and Rodenticide Act as amended, for the pesticide registered under EPA Reg. No. 100-740

Dividend®
Fungicide

A seed treatment for control of diseases of cereals

For use only by commercial seed treaters

Active Ingredient:
[(2S,4R)/(2R,4S)]/[(2R,4R/2S,4S)]
1-[2-[4-(4-Chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl]-1H-1,2,4-triazole ... 32.8%
Inert Ingredients: 67.2%
Total: 100.0%

[redacted] U.S. Standard Measure

30 Gallons
U.S. Standard Measure

KEEP OUT OF REACH OF CHILDREN.

CAUTION

See additional precautionary statements and directions for use inside booklet.

EPA Reg. No. 100- EPA Est. 100-

CGA 128L1 (gals.)
CGA 128L3 (30 gals.)

DIRECTIONS FOR USE AND CONDITIONS OF SALE AND WARRANTY

IMPORTANT: Read the entire Directions for Use and the Conditions of Sale and Warranty before using this product. If the terms are not acceptable, return the unopened product container at once.

Conditions of Sale and Warranty

The Directions for Use of this product reflect the opinion of experts based on field use and tests. The directions are believed to be reliable and should be followed carefully. However, it is impossible to eliminate all risks inherently associated with use of this product. Crop injury, ineffectiveness, or other unintended consequences may result because of such factors as weather conditions, presence of other materials, or the manner of use or application, all of which are beyond the control of Ciba-Geigy or the Seller. All such risks shall be assumed by the Buyer.

Ciba-Geigy warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes referred to in the Directions for Use subject to the inherent risks referred to above. Ciba-Geigy makes no other express or implied warranty of Fitness or Merchantability or any other express or implied warranty. In no case shall Ciba-Geigy or the Seller be liable for consequential, special, or indirect damages resulting from the use or handling of this product. Ciba-Geigy and the Seller offer this product, and the Buyer and user accept it, subject to the foregoing Conditions of Sale and Warranty, which may be varied only by agreement in writing signed by a duly authorized representative of Ciba-Geigy.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Not for use on agricultural establishments in hopper-box, planter-box, slurry-box, or other seed treatment applications at or immediately before planting.

FAILURE TO FOLLOW THE DIRECTIONS FOR USE AND PRECAUTIONS ON THIS LABEL MAY RESULT IN CROP INJURY, POOR DISEASE CONTROL, AND/OR ILLEGAL RESIDUES.

General Information

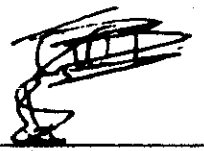
Dividend is a systemic seed dressing which controls or suppresses certain seed-borne, soil-borne, and fall season foliar diseases of wheat. An EPA-approved coloring agent, Pigment Red 48, has been added to the formulation.

Mixing Procedures

Dividend should be applied as a [redacted] through standard slurry or mist-type commercial seed treaters. Prepare a slurry by mixing Dividend in up to 16 fl. oz. of water per 100 lbs. of seed. Mix the slurry thoroughly with the seed to provide uniform coverage.

Wheat

Apply Dividend to wheat seed at the rates given in the table below for control of [redacted]



DIVIDEND
Winter Wheat

Rate/CWT	Diseases Controlled	Fall Season Foliar Diseases Controlled[1]	Diseases Partially Controlled[2]
1 fl. oz.	Common Bunt[3] Drawf Bunt Loose Smut Flag Smut Seed borne Septoria General Seed Rots[4] Fusarium Seed Scab	Fall Season Powdery Mildew Fall Season Leaf Rust Fall Season Septoria Leaf Blotch Fall Season Stripe Rust	Common Foot Rot (*Cochliobolus spp.*) Fusarium Root Rot Fusarium Crown Rot Take-All
1/2 fl. oz.	Common Bunt[3] Dwarf Bunt Flag Smut Seed-borne Septoria Loose Smut General Seed Rots[4] Fusarium Seed Scab		Common Foot Rot *(Cochlibolus spp.)*
1/4 fl. oz.[5]	Common Bunt Loose Smut		

[1]Dividend provides control of fall season powdery mildew, fall season leaf rust, fall stripe rust, and fall season Septoria leaf blotch in winter wheat for the first six weeks after planting. For full season control of these foliar diseases, use Tilt® fungicide according to label instructions.

[2]Partial control can either mean erratic control from good to poor or consistent control at a level below that generally considered acceptable for commercial disease control.

[3]Dividend controls both seed-borne and soil-borne common bunt.

[4]General seed rots controlled include those causes by saprophytic organisms such as Penicillium and Aspergillus.

[5]The 1/4 fl. oz. rate should only be used in the following states: Texas, Oklahoma, Kansas, Colorado, Missouri, Nebraska, North Dakota, South Dakota, Minnesota, Montana.

DIVIDEND
Spring Wheat

Rate/CWT	Diseases Controlled
1/2 fl. oz.	Common Bunt Seed-borne Septoria Loose Smut General Seed Rots[2] Fusarium Seed Scab
1/4 fl. oz.[3]	Common Bunt Loose Smut

[1]Dividend controls both seed-borne and soil-borne common bunt.

[2]General seed rots controlled include those causes by saprophytic organisms such as Penicillium and Aspergillus.

[3]The 1/4 fl. oz. rate should only be used in the following states: Texas, Oklahoma, Kansas, Colorado, Missouri, Nebraska, North Dakota, South Dakota, Minnesota, Montana.

Important: (1) Do not use treated seed for feed, food or oil [redacted]

[redacted] Federal law requires that bags containing treated seeds shall be labeled with the following information: "This seed has been treated with difenoconazole fungicide. Do not use for feed, food, or oil purposes. Store away from feeds and foodstuffs." If necessary, use with an EPA-approved dye or colorant that imparts an unnatural color to the seed.

Storage and Disposal

Pesticide Storage and Disposal

Do not contaminate water, food, or feed by storage, disposal or cleaning of equipment. Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

(For one gallon)

Container Disposal

Do not reuse empty container. Triple rinse (or equivalent), then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, by incineration, or by open burning, if allowed by state and local authorities. If burned, keep out of smoke.

(For 30 gallons)

Container Refilling and Disposal

Refer to label on container for refilling and disposal instructions.

For minor spills, leaks, etc., follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup and disposal of wastes. In the event of a major spill, fire, or other emergency, call 1-800-888-8372, day or night.

Precautionary Statements

Hazards to Humans and Domestic Animals

CAUTION

Causes moderate eye irritation. Avoid contact with eyes or clothing. Harmful if inhaled or absorbed through skin. Avoid breathing vapor or spray mist. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Statement of Practical Treatment

If in eyes: Flush eyes with plenty of water. Get medical attention if irritation persists.

If inhaled: Move victim to fresh air.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

Note to Physician: If ingested, induce emesis or lavage stomach. Treat symptomatically.

Environmental Hazards

This product is toxic to fish and other aquatic wildlife. Keep out of lakes, streams, ponds, tidal marshes and estuaries. For terrestrial uses, do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment wash waters or rinsates.
If treated seed is spilled outdoors or in areas accessible to birds, promptly clean up or bury to prevent ingestion.

Dividend® trademark of Ciba-Geigy Corporation
U.S. Patent No. 5,266,585

Ciba Crop Protection
Seed Treatment Products
Ciba-Geigy Corporation
Greensboro, North Carolina 27419

CGA 128L1 (gals.)
CGA 128L3 (30 gals.)

[GANNONC.LABELD\LBL-D-MS-WORD]DIVID-A - 6/30/94

(For 1 Gallon)
Pressure-Sensitive Label
Master Label

Dividend®
Fungicide

A seed treatment for control of diseases of cereals

For use only by commercial seed treaters

Active Ingredient:	
1-{2-[4-(4-Chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1H-1,2,4-triazole	32.8%
Inert Ingredients:	67.2%
Total:	100.0%

See directions for use in attached booklet.

One Gallon
U. S. Standard Measure

KEEP OUT OF REACH OF CHILDREN.

CAUTION

Precautionary Statements

Hazards to Humans and Domestic Animals

Causes moderate eye irritation. Avoid contact with eyes or clothing. Harmful if inhaled or absorbed through skin. Avoid breathing vapor or spray mist. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Statement of Practical Treatment

If in eyes: Flush eyes with plenty of water. Get medical attention if irritation persists.

If inhaled: Move victim to fresh air.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

Note to Physician: If ingested, induce emesis or lavage stomach. Treat symptomatically.

Environmental Hazards

This product is toxic to fish and other aquatic wildlife. Keep out of lakes, streams, ponds, tidal marshes and estuaries. For terrestrial uses, do not apply directly to water, or to areas where surface water present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment wash waters or rinsates.

If treated seed is spilled outdoors or in areas accessible to birds, promptly clean up or bury to prevent ingestion.

Dividend® trademark of Ciba-Geigy Corporation
U.S. Patent No. 5,266,585

EPA Reg. No. 100- EPA Est. 100-

Ciba Crop Protection
Seed Treatment Products
Ciba-Geigy Corporation
Greensboro, North Carolina 27419

CGA 128L1

Ciba

[GANNONC.LABELD\LBL-D-MS-WORD]DIVID-A - 6/30/94

June 30, 1994- Corrected plant back statement, added PR93-11 statement for seed trt., Crop Protection, 30 gallon refillable

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
401 "M" St., S.W.
Washington, D.C. 20460

NOTICE OF PESTICIDE:
_X_ Registration
____ Reregistration
(under FIFRA, as amended)

EPA Reg. Number:	Date of Issuance:
100-740	

Term of Issuance: Conditional

Name of Pesticide Product: Dividend Fungicide

Name and Address of Registrant (include ZIP Code):

Ciba-Geigy Corporation
P.O. Box 18300
Greensboro, NC 27419-8300

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA sec. 3(c)(7)(C) provided that you:

1. Submit by December 31, 1998 the following Studies conducted on accordance with the Good Laboratory Practice Standards, 40 CFR Part 160 and appropriate test guidelines as referenced in EPA's Data Requirements for Registration Regulations, 40 CFR Part 158:

   a. Stability of the Technical Grade Active Ingredient (TGAI)to Metal Ions Study [Guideline Line Number (GLN) 63-13]

   b. Storage Stability of Difenoconazole in other Raw Agricultural Commodities [GLN 171-4(e)]

   c. Additional Wheat Field Residue Trials [GLN 171-4(k)].

2. Make the following label changes listed below before you release the product for shipment:

   a. Add the phrase, "EPA Reg. No. 100-740".

   b. On the front panel delete "cereals" and specify "wheat".

Signature of Approving Official:	Date:
/S/	8-3-94

EPA Form 8570-6

c. Modify the Environmental Hazard Statement so it reads as follows:

> This product is toxic to fish and aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when disposing of equipment washwaters or rinsate.

d. On the 30 gallon container label, if the precautionary statements do not appear on the front panel, add, in close proximity to the Signal Word CAUTION, a referral statement to see side panel for additional precautionary statements.

3. Submit production information (pounds or gallons produced) for this product for the fiscal year in which the use on wheat is conditionally registered, in accordance with FIFRA section 29. The fiscal year begins October 1, and ends September 30. The product information will be submitted to the Agency no later than November 15, following the end of the preceding fiscal year.

This information is to be submitted to:

> Registration Support Branch
> Registration Division (7505W)
> Environmental Protection Agency
> Washington, DC 20460

4. Submit one (1) copy of your final printed labeling before you release the product for shipment. Refer to the A-79 enclosure for a further description of final printed labeling.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Cynthia Giles-Parker
Product Manager (22)
Fungicide-Herbicide Branch
Registration Division (7505C)

Enclosure

Technical CGA-169374

For Formulation into
End-Use Fungicide Products

Active Ingredient: Difenoconazole (CAS #119446)	[redacted]
Other Ingredients:	5.0%
Total:	100.0%

110.1 Pounds (50 Kg) Net Weight or 88.2 Pounds (40 kg) Net Weight

EPA Reg. No. 100-739 EPA Est. 34630-SW-1

KEEP OUT OF REACH OF CHILDREN.

CAUTION

Precautionary Statements

Hazards to Humans and Domestic Animals

Harmful if swallowed, inhaled, or absorbed through skin. Causes moderate eye irritation. Avoid contact with skin, eyes, or clothing. Avoid breathing vapor or spray mist. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Statement of Practical Treatment

If swallowed: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching the back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

If in eyes: Flush eyes with plenty of water. Get medical attention if irritation persists.

If inhaled: Move victim to fresh air.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

ACCEPTED
with COMMENTS
In EPA Letter Dated
MAY 18 1998
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide registered under EPA Reg. No. 100-739

Note to Physician: If ingested, induce emesis or lavage stomach. Treat symptomatically.

Environmental Hazards

This product is toxic to fish and other aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

DIRECTIONS FOR USE AND CONDITIONS OF SALE AND WARRANTY

IMPORTANT: Read the entire **Directions for Use** and the **Conditions of Sale and Warranty** before using this product. If the terms are not acceptable, return the unopened product container at once.

CONDITIONS OF SALE AND WARRANTY

The **Directions for Use** of this product reflect the opinion of experts based on field use and tests. The directions are believed to be reliable and should be followed carefully. However, it is impossible to eliminate all risks inherently associated with use of this product. Crop injury, ineffectiveness, or other unintended consequences may result because of such factors as weather conditions, presence of other materials, or the manner of use or application, all of which are beyond the control of Novartis Crop Protection, Inc. or the Seller. All such risks shall be assumed by the Buyer.

Novartis warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes referred to in the **Directions for Use** subject to the inherent risks referred to above. **Novartis makes no other express or implied warranty of Fitness or Merchantability or any other express or implied warranty. In no case shall Novartis or the Seller be liable for consequential, special, or indirect damages resulting from the use or handling of this product.** Novartis and the Seller offer this product, and the Buyer and user accept it, subject to the foregoing **Conditions of Sale and Warranty**; which may be varied only by agreement in writing signed by a duly authorized representative of Novartis.

No end use of this product other than formulation is intended or implied by the above Conditions of Sale and Warranty.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Chemical and Physical Properties

Refer to Technical Bulletin for Technical CGA-169374.

Storage and Disposal

Pesticide Storage and Disposal

Do not contaminate water, food, or feed by storage, disposal or cleaning of equipment. Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

Container Disposal

Completely empty liner by shaking and tapping sides and bottom to loosen clinging particles. Empty residue into application equipment. Then dispose of liner in a sanitary landfill or by incineration, if allowed by state and local authorities. If drum is contaminated and cannot be reused, dispose of in the same manner.

For minor spills, leaks, etc., follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup and disposal of wastes. In the event of a major spill, fire, or other emergency, call 1-800-888-8372, day or night.

U.S. Patent No. 5,266,585

Novartis Crop Protection, Inc.
Greensboro, North Carolina 27419

NCP 739A-L2A 0498 (50 kg)
NCP 739A-L5A 0498 (40 kg)

[LABELC-W]N-C169374T - ccg - 4/8/98

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MAY 18 1998

Mr. Richard Pence
Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, North Carolina 27419-8300

Subject: Technical CGA-169374
EPA Registration No. 100-739
Your amended label dated April 14, 1998

Dear Mr. Pence,

The labeling referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, is acceptable provided that you:

1. Make the following changes to the product label:

   a. In the first sentence in the Environmental Hazards section on the second to the last page in the subject label delete "other" from before "aquatic invertebrates"; fish are not invertebrates.

   b. In the Environmental Hazards section, at the end of the last sentence change "EPA" to Environmental Protection Agency".

   c. In the Directions for Use section, add a statement that begins "Only [redacted]

2. Submit the Technical Bulletin referred to in the "Chemical and Physical Properties" section of the label to the Agency for review. Since the bulletin is referred to in the labeling, it is therefore a part of the labeling, and subject to review. Alternatively, the reference to the Technical Bulletin could be dropped.

3. Submit one copy of your final printed labeling before you release the product for shipment.

If these conditions are not complied with, the registration may be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product bearing the amended labeling constitutes acceptance of these conditions.

A stamped copy of the labeling is enclosed for your records.

Sincerely yours,

/s/

Cynthia L. Giles-Parker
Product Manager (22)
Fungicide Branch
Registration Division (7505C)

Attachment: Label stamped "Accepted with Comments"

13544

R125886

Chemical: Difenoconazole

PC Code:
128847

HED File Code: 14000 Risk Reviews
Memo Date: 11/25/1998
File ID: 00000000
Accession #: 412-06-0194

HED Records Reference Center
8/8/2006